THALIDOMIDE: POTENTIAL BENEFITS AND RISKS

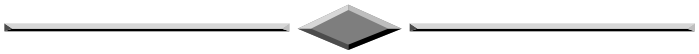
AN OPEN PUBLIC SCIENTIFIC WORKSHOP

Program and Abstracts

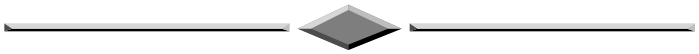
Office of the Director
National Institutes of Health

Thalidomide: Potential Benefits and Risks

Open Public Scientific Workshop



September 9-10, 1997
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland



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National Institutes of Health: • Office of Rare Diseases • Office of Research on Women's Health • Office of Medical Applications of Research • National Institute of Allergy and Infectious Diseases • National Institute of Arthritis and Musculoskeletal and Skin Diseases • National Institute of Dental Research • National Institute of Child Health and Human Development • National Institute of Mental Health

Food and Drug Administration: • Center for Drug Evaluation and Research • Office of Special Health Issues • Office of Orphan Products Development

Centers for Disease Control and Prevention

Welcome

William R. Harlan, M.D.

This is an important and timely meeting that is intended to evaluate the promising research and clinical applications of thalidomide. The promise of this agent must be balanced with the known toxicity and the accompanying ethical and legal constraints on this use. The workshop is designed to assess the benefits and risks and to guide further investigation and clinical use.

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Thalidomide: Potential Benefits and Risks

The introduction of thalidomide into the marketplace in the 1950s as treatment for insomnia and morning sickness was responsible for the occurrence of more than 10,000 reported cases of birth defects. Birth defects observed in babies exposed to thalidomide during pregnancy include missing or abnormal legs, arms, feet, and hands; spinal cord defects, cleft lip or palate, absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system.

Recent research suggests potential activity of thalidomide as an adjunctive treatment in numerous serious medical conditions. Because of its pharmacological properties, thalidomide has been reintroduced into the research community for treatment of complications of infectious diseases, autoimmune and skin disorders, and several types of cancer. The risks related to thalidomide remain essentially the same today as when the product was originally marketed in more than 45 countries almost 40 years ago; however, as various patient populations are exposed, more side effects may be seen.

Ongoing research continues to investigate the numerous uses of thalidomide in conditions such as erythema nodosum leprosum, lupus erythematosus, chronic graft-versus-host disease, gliomas, and infectious diseases including tuberculosis, aphthous ulcers, and the wasting syndrome associated with HIV infection. More than 1,000 patients in the United States are already using thalidomide either on an FDA authorized compassionate use basis or in clinical research trials. Women of childbearing potential who are participating in the research of this compound are required to use multiple contraceptives or to have been previously sterilized. Women of childbearing potential involved in clinical research investigations are required to have monthly pregnancy tests before, during, and after the course of thalidomide treatment if they are experiencing a normal menstrual cycle and more frequently if the menstrual cycle is irregular. This testing is based on a susceptibility window described in the medical literature as occurring between days 35 and 50 after a woman's last menstrual period—the time during which the development of the fetus is at risk for thalidomide-associated malformations. It is unknown whether thalidomide may cause birth defects in the unborn if it is taken outside of this timeframe.

The National Institutes of Health together with the Food and Drug Administration and the Centers for Disease Control and Prevention are sponsoring a workshop, Thalidomide: Potential Benefits and Risks, to be held in Bethesda, Maryland, on September 9-10, 1997. There are several objectives for this workshop. The first objective is to provide a public forum for assessing the emerging research opportunities, potential clinical applications, and the accompanying known and unknown risks of taking thalidomide. The second objective is to provide effective risk-communication and risk-management procedures to the relevant health care providers and patients about the potential benefits and risks associated with the use of thalidomide in the community and research environment. Finally, the workshop will present current methods for monitoring safety and adverse effects.

Research is focusing on thalidomide's unique pharmacological and immunological properties. Thalidomide has been shown to have antiangiogenic properties in preclinical studies. Theoretically, this property may have important implications for the developing embryo, tumor growth with metastatic spread, and macular degeneration. Thalidomide's role as a tumor necrosis factor (TNF)-alpha inhibitor is under investigation. Thalidomide's immunologic effects may help to mediate disease states where TNF-alpha is produced and in excess such as HIV disease and tuberculosis.

Many research questions remain unanswered. Will research with thalidomide produce pharmacologically active analogues without the accompanying teratogenic, peripheral neurologic, and sedative effects? Some investigators have suggested that thalidomide may be mutagenic. Has this potential risk been adequately studied? It is not known whether thalidomide is present in male ejaculate (semen). What effects, if any, would its presence have on a child fathered by a patient on thalidomide?

Numbness or tingling in the arms, hands, legs, and feet due to peripheral neuropathy or nerve damage usually occurs after long-term use of the drug but can occur after brief exposure to the drug. Is the nerve damage permanent or will it resolve after use of the drug has been discontinued? Thalidomide also causes drowsiness that can be of concern to patients participating in clinical trials. Would a reduction in the thalidomide dosage reduce drowsiness while maintaining clinical effectiveness?

To address these issues, the workshop will bring together specialists in the behavioral sciences, dentistry, dermatology, epidemiology, immunology, infectious diseases, law, bioethics, medicine, neurology, oncology, pharmacology, pharmacy, psychiatry, regulatory scientists, toxicology, and patient advocacy and women's health issues to discuss these questions. The speakers will present reviews of the current state of scientific knowledge regarding the potential benefits and risks of thalidomide. Scientific studies to assess the safety and efficacy in many of the areas are ongoing. This workshop will discuss the current state of scientific knowledge and future research to attempt to resolve many of the unanswered questions that remain. The meeting will also serve as an opportunity to communicate information regarding risks and potential benefits of thalidomide to patients and health care providers, and the public at large.

One strong and continuing public health message must be clearly communicated to the American people and the people of the world. Despite the potential therapeutic benefits to selected patient populations with serious and life-threatening diseases, thalidomide is a drug with serious risks that cannot be ignored or taken lightly.

Agenda

Tuesday, September 9, 1997

I. Opening Remarks and Overview

Moderator: Stephen C. Groft, Pharm.D., Office of Rare Diseases, NIH

8:30 a.m.	Opening Remarks and Introductions **Stephen C. Groft, Pharm.D.,** Director, Office of Rare Diseases, NIH
8:40 a.m.	Welcome **William R. Harlan, M.D.,** Associate Director for Disease Prevention, NIH
8:50 a.m.	Historical Perspective **Frances O. Kelsey, M.D.,** Deputy for Scientific Affairs, Office of Compliance, Center for Drug Evaluation and Research, FDA
9:10 a.m.	Current Issues and Overview **Janet Woodcock, M.D.,** Director, Center for Drug Evaluation and Research, FDA
9:25 a.m.	Experience With Thalidomide in Mexico **Guillermo Bierzwinsky Snieder, M.D.,** Director, Drug Control Directorate of Mexico
9:40 a.m.	Clinical Pharmacology of Thalidomide **Carol Braun Trapnell, M.D.,** Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, FDA
9:55 a.m.	Ethical Issues in the Use of Thalidomide in Fertile Women **Norman Fost, M.D., M.P.H.,** University of Wisconsin-Madison
10:10 a.m.	Report on Meeting of Dermatologic and Ophthalmic Drugs Advisory Committee **Jonathan Wilkin, M.D.,** Director, Division of Dermatologic and Dental Drug Products, Center for Drug Evaluation and Research, FDA
10:20 a.m.	Questions
10:30 a.m.	Break

II. Perspectives From the Public—A Consultation With...

Moderator: Theresa Toigo, R.Ph., M.B.A., Associate Commissioner for Special Health Issues, FDA

10:45 a.m.	**Leo J. Yoder, M.D.,** American Leprosy Missions Perspectives from the Public—A Consultation With. . .
10:55 a.m.	**Randolph Warren**, Thalidomide Victims' Association of Canada Thalidomide: The Survivor's Perspective
11:05 a.m.	**William A. Zellmer, M.P.H.,** American Society of Health-System Pharmacists Pharmacist's Perspective
	James Allen, M.D., American Medical Association Physician's Perspective
11:25 a.m.	**Cynthia Pearson**, National Women's Health Network Thoughts About Thalidomide: Are We Now and Can We Ever Be Ready for the Mainstreaming of Thalidomide?
11:35 a.m.	**Nancy Paller** A Personal Perspective
11:45 a.m.	Questions and Discussion
Noon	Lunch

Tuesday, September 9 (continued)

III. Monitoring for Safety and Management of Adverse Events

Moderator: Debra Birnkrant, M.D., Division of Anti-Viral Drug Products, Center for Drug Evaluation and Research, FDA

1:00 p.m. Protection of Human Subjects Involved in Thalidomide Research—The Role of the Institutional Review Boards
Melody Lin, Ph.D., Office for Protection from Research Risks, NIH

1:15 p.m. Regulatory Considerations in the Clinical Development of Thalidomide: Safety Monitoring and Investigational Safety Findings
Debra Birnkrant, M.D., Division of Anti-Viral Drug Products, Center for Drug Evaluation and Research, FDA

1:30 p.m. Thalidomide Neuropathy
Herbert H. Schaumburg, M.D., Albert Einstein College of Medicine

1:45 p.m. Peripheral Neuropathy and Exposure to Thalidomide
Colin Crawford, M.R.C.P., D.P.M.&H., Imperial College of Science, Technology and Medicine, London

2:00 p.m. Neurological Testing of Primates
Tucker A. Patterson, Ph.D., National Center for Toxicological Research, FDA

2:15 p.m. Monitoring for Peripheral Neuropathy
Mary K. Floeter, M.D., Ph.D., National Institute of Neurological Disorders and Stroke, NIH

2:30 p.m. Questions and Discussion

2:45 p.m. Break

IV. Pregnancy/Embryopathy

Moderator: James Mills, M.D., National Institute of Child Health and Human Development, NIH

3:00 p.m. Characterization of Embryopathy Risks
Barbara A. Hill, Ph.D., Division of Dermatological and Dental Drug Products, Center for Drug Evaluation and Research, FDA

3:15 p.m. Pregnancy Prevention in Patients Taking Thalidomide
Christine K. Mauck, M.D., M.P.H., Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research, FDA

3:30 p.m. How Environmental Effects on Child Health Are Recognized
Robert W. Miller, M.D., Dr.P.H., National Cancer Institute, NIH

3:45 p.m. Experience With Accutane
Allen A. Mitchell, M.D., Boston University

4:00 p.m. Preventing Birth Defects Due to Thalidomide Exposure
Cynthia Moore, M.D., Ph.D., Centers for Disease Control and Prevention

4:15 p.m. Questions and Discussion

Wednesday, September 10

V. Risk Management

Moderator: Louis A. Morris, Ph.D., Chief, Division of Drug Marketing, Advertising, and Communications, Center for Drug Evaluation and Research, FDA

8:00 a.m. Effective Risk Communication
Louis A. Morris, Ph.D., Division of Drug Marketing, Advertising, and Communications, Center for Drug Evaluation and Research, FDA

8:15 a.m. Role of Communication To Influence Behavior
Martin Fishbein, Ph.D., University of Pennsylvania

8:30 a.m. Clinical Ethical Considerations in the Use of Thalidomide: A Practitioner's Perspective
Gail J. Povar, M.D., M.P.H., F.A.C.P., George Washington University School of Medicine

8:45 a.m. Patients' Rights and Physicians' Responsibilities
Mark Senak, J.D., AIDS Project Los Angeles

9:00 a.m. Risk Management—Educational, Advertising, and Marketing Efforts: Industry Perspectives
Bruce A. Williams, Celgene Corporation

9:15 a.m. Questions and Discussion

VI. Perspectives on Present and Future Needs

Moderator: Ann Ginsberg, M.D., National Institute of Allergy and Infectious Diseases, NIH

9:30 a.m. Research Perspective
Gilla Kaplan, Ph.D., The Rockefeller University

9:45 a.m. Thalidomide: Bioethical and Legal Issues—Industry's Perspective on Present and Future Needs
Peter Andrulis, Ph.D., Andrulis Pharmaceuticals Corporation

10:00 a.m. Legal Perspective
Frank C. Woodside III, M.D., J.D., Dinsmore & Shohl

Thalidomide Revisited—The Nightmare To Come
Thomas H. Bleakley, J.D., Bleakley and McKeen, PC

10:30 a.m. Questions and Discussion

VII. Concurrent Sessions on Scientific Advances, Pharmacology, Potential Clinical Applications, and Research Trends for Thalidomide

Section A
10:45 a.m. Pharmacology, Pharmacokinetics, and Teratology of Thalidomide and Analogues
Chair: J. David Erickson, D.D.S., Ph.D., Centers for Disease Control and Prevention

Thalidomide: A Molecular Template for Drug Discovery
David Stirling, Ph.D., Celgene Corporation

Pharmacology, Pharmacokinetics, and Teratology of Thalidomide and Analogues
Edward J. Shannon, Ph.D., G.W. Long Hansen's Disease Center, Louisiana State University

Carol Braun Trapnell, M.D., Office of Therapeutic Research and Review, Center for Biologics Evaluation and Research, FDA

Wednesday, September 10 (continued)

Section B
10:45 a.m.

Dermatology
Chair: Mervyn L. Elgart, M.D., George Washington University School of Medicine

Thalidomide for the Treatment of Prurigo Nodularis of HIV-Infected Patients
Toby A. Maurer, M.D., University of California at San Francisco

Erythema Nodosum Leprosum
Thomas H. Rea, Jr., M.D., University of Southern California, Los Angeles County Hospital

Thalidomide for Behçet's Disease and Complex Aphthosis
Alan B. Fleischer, Jr., M.D., Bowman Gray School of Medicine, Wake Forest University

Thalidomide in Pyoderma Gangrenosum
Mervyn L. Elgart, M.D., George Washington University School of Medicine

Section C
10:45 a.m.

Immunology/Rheumatology
Chair: Philip Fox, D.D.S., National Institute of Dental Research, NIH

Discoid and Systemic Lupus Erythematosus
John H. Klippel, M.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

A Pilot Study of Thalidomide for Primary Sjögren's Syndrome
Stanley R. Pillemer, M.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH

Treatment of Rheumatoid Arthritis With Thalidomide
Sicy Lee, M.D., Hospital for Joint Diseases

The Potential Application of Thalidomide for the Treatment of Inflammatory Bowel Disease
Robert H. Gelber, M.D., University of California, San Francisco

Section D
10:45 a.m.

Hematology/Oncology
Chair: James Pluda, M.D., National Cancer Institute, NIH

A Phase II Trial of the Antiangiogenic Agent Thalidomide in Patients With Recurrent High-Grade Gliomas
Howard A. Fine, M.D., Dana-Farber Cancer Institute

A Randomized Phase II Study of Thalidomide in Androgen-Independent Prostate Cancer
William D. Figg, Pharm.D., National Cancer Institute, NIH

Thalidomide Treatment of Graft-Versus-Host Disease
Georgia B. Vogelsang, M.D., Johns Hopkins University

Preliminary Results of a Phase II Dose Titration Study of Oral Thalidomide in Patients With HIV Infection and Kaposi's Sarcoma
Robert Yarchoan, M.D., National Cancer Institute, NIH

Phase II Evaluation of Thalidomide in Patients With Metastatic Breast Cancer
Said Baidas, M.D., Georgetown University, School of Medicine

Wednesday, September 10 (continued)

Section E 10:45 a.m.	Infectious Diseases **Chair: Lawrence Fox, M.D., Ph.D.,** National Institute of Allergy and Infectious Diseases, NIH
	Thalidomide as Immunomodulatory Adjunctive Therapy in Tuberculosis **Gilla Kaplan, Ph.D.,** The Rockefeller University
	HIV/AIDS Wasting Syndrome **Morris Schambelan, M.D.,** University of California, San Francisco
	Thalidomide for the Treatment of Oral Aphthous Ulcers in Patients With Human Immunodeficiency Virus Infection **Jeffrey Jacobsen, M.D.,** Bronx Veterans' Administration Hospital
	The Neurology of AIDS **Howard E. Gendelman, M.D.,** University of Nebraska Medical Center
12:45 p.m.	Lunch
2:00 p.m.	Open Public Session **Chair: Stephen C. Groft, Pharm.D.,** Office of Rare Diseases, NIH Panel: Session Moderators
3:00 p.m.	Responses From Workshops on Research Advances and Opportunities **Chair: Stephen C. Groft, Pharm.D.,** Office of Rare Diseases, NIH
3:45 p.m.	Discussion
4:00 p.m.	Closing Remarks **Janet Woodcock, M.D.,** Director, Center for Drug Evaluation and Research, FDA
4:15 p.m.	Adjournment

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Abstracts

The following abstracts of presentations to the Workshop on Thalidomide: Potential Benefits and Risks were furnished by speakers in advance of the workshop. Abstracts for the following presentations do not appear:

Physician's Perspective - James Allen, M.D.

Role of Communication To Influence Behavior - Martin Fishbein, Ph.D.

Protection of Human Subjects Involved in Thalidomide Research(The Role of the

Institutional Review Boards - Melody Lin, Ph.D.

Effective Risk Communication - Louis A. Morris, Ph.D.

A Personal Perspective - Nancy Paller

Patients' Rights and Physicians' Responsibilities - Mark Senak, J.D.

This book is designed for the use of participants in the workshop and as a pertinent reference document for anyone interested in the workshop subject. We are grateful to the authors who have summarized their materials and made them available in a timely fashion.

Stephen C. Groft, Pharm.D.
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Bethesda, MD

Historical Perspective

Frances O. Kelsey, M.D.

On September 12, 1960, the New Drug Branch of the Bureau of Medicine (a forerunner of the Food and Drug Administration's Center for Drug Evaluation and Research) received a New Drug Application (NDA 12-611) for the drug thalidomide. The indications for use were as a mild hypnotic and sedative. At that time, thalidomide was widely used elsewhere, particularly in Europe, either as a single drug or in combination with other drugs. It was considered so safe that it was available without prescription in many areas.

Under the 1938 Food, Drug and Cosmetic Act then in effect, the sponsor of a New Drug Application was required only to show a drug was safe when used as labeled—efficacy did not have to be established. The agency had 60 days to review the supporting chemical control data and the pharmacologic and clinical findings. If the agency reported no adverse findings within this timeframe, the application became effective. The 1938 law permitted unapproved drugs to be shipped in interstate commerce for clinical trials provided they were clearly labeled for investigational use only, that they were distributed only to qualified individuals who signed a statement certifying they had the facilities to test the drug, and that the sponsoring firm kept a record of all persons to whom the drug had been sent. It was not necessary for the sponsor to notify the agency that the drug was under clinical trial or to report the results of the clinical trials unless a New Drug Application was subsequently submitted to the agency.

The thalidomide application was reviewed by a chemist, a pharmacologist, and a medical officer, the process still followed by the FDA. All three reviewers found serious shortcomings. Additional data were submitted, but further safety concerns were prompted by reports from Europe, which reached the Agency in February 1961, of peripheral neuritis developing in patients receiving the drug for prolonged periods. These concerns included the possible adverse effects on the fetus if the drug were to be taken during pregnancy.

At the end of November 1961, the sponsor notified the agency that studies with thalidomide were being halted pending further information from Germany, where the drug had been withdrawn from the market following a reported association between the use of the drug and a rare birth defect, phocomelia. The application was not withdrawn, however, because the sponsor wished to continue some ongoing studies on the possible value of the drug in the treatment of cancer. In March 1962, the New Drug Application was officially withdrawn.

The underlying concerns of the three FDA reviewers will be reviewed, and the role of the thalidomide episode in ensuring the passage of the 1962 amendments to the 1938 law and the 1963 Investigational New Drug Regulations will be discussed.

Experience With Thalidomide in Mexico

Guillermo Bierzwinsky, M.D.

Thalidomide was first synthesized by Kunz in 1956 in Germany (Kunz et al., 1956). It was initially used as a sedative in various countries (Mellin and Katzenstein, 1962). Reports of peripheral neuritis in 1960 (Burley, 1961; Fullerton and Kremer, 1961) delayed approval of thalidomide by the FDA. In late 1961, the possible association between unexplained fetal abnormalities and the use of thalidomide was raised by Lenz at a meeting in Westphalia. The manufacturer withdrew the drug from the market in l961. The tragedy of thalidomide is largely responsible for the strict sanitary regulations applied presently for approval of new drugs in several countries. However, positive actions of thalidomide have also been observed.

In l965, Sheskin (1965) serendipitously noted improvement with thalidomide use in the inflammatory reaction of leprosy patients known as erythema nodosum leprosum (ENL), and since then thalidomide has become the drug of choice for its treatment. In Mexico, thalidomide was licensed for this indication in 1988.

Thalidomide has also been successfully used for the treatment of other difficult ailments like Behçet's disease, lupus erythematosus, graft-versus-host disease, ulcerative colitis (Koch, 1985; D'Arcy, Griffen, 1994), and esophageal ulcers in AIDS (Ryan, Colman, Pedersen, et al., 1992).

More recently, there has been interest in the use of thalidomide in the treatment of certain aspects of the clinical picture of AIDS. Mexico ranks in third place in the number of AIDS cases in the American Continent and eleventh in the world (SIDA, Mexico, 1991).

It has been shown that thalidomide has no antibacterial effects in cases of ENL (Sheskin, Sagher, Dorfman, et al., 1968). This and other observations suggest that its beneficial effects are exerted through a direct action on the immune system, as supported by the suppression of graft-versus-host disease (GVHD) observed in animal experiments and in humans (Field, Gibbs, Tucker, et al., 1966). It has been reported to selectively inhibit the production of tumor necrosis factor-alpha (TNF-() by human peripheral blood mononuclear cells (PBMCs) (Sampaio, Sarno, Galilly, et al., 1991), primarily by accelerating the degradation of TNF-(messenger RNA transcripts (Moreira, Sampaio, Zmuidzinas, et al., 1993). Also, thalidomide inhibits in vitro both TNF-(mRNA and TNF-(protein, as well as the expression of HIV-1 in infected cell lines and in PBMCs of infected patients (Makonkawkeyoon, Limson-Pobre, Moreira, et al., 1993).

Human immunodeficiency virus (HIV) disease has detrimental effects on the nutritional status of infected patients (Gorbach, Knox, Roubenoff, 1993). Progressive weight loss is a major clinical feature and a diagnostic criterion of AIDS (Council of State and Territorial Epidemiologists, 1987) and contributes to its morbidity and mortality (Kotler, Wang, Pierson, 1989) independent of CD4+ T cell counts (Guenter, Muurahainen, Simons, et al., 1993). Weight loss in these patients is at the expense of body cell mass, predominantly of muscle protein (wasting or cachexia) (Kotler, Wang, Pierson, 1985) and may occur in two patterns during the late

clinical stage of HIV disease: (1) acute, severe, and remitting weight loss, mostly related to opportunistic infections and (2) chronic, progressive weight loss, the wasting syndrome (Macallan, Noble, Baldwin, et al., 1993).

At the Instituto Nacional de la Nutrición Salvador Zubirán in Mexico, a randomized, double-blind, placebo-controlled trial was designed to evaluate the efficacy of thalidomide (Klausner, Makonkawkeyoon, Akarasewi, et al., 1994), a selective inhibitor of tumor necrosis factor alpha (TNF-(), in the treatment of wasting syndrome in patients with advanced HIV disease, and to assess the effects of thalidomide on peripheral CD4+ T cells, plasma levels of TNF-(, and HIV viral burden in PBMCs. Patients included were adults with an advanced HIV disease, under antiretroviral therapy, without an active opportunistic infection, and with (10 percent of weight loss in the previous 6 months. Patients were stratified by severity of weight loss and CD4+ T cell count and assigned in a random and double-blinded fashion to receive thalidomide (100 mg four times daily) or a matching placebo. Patients were followed for 12 weeks.

Weight and anthropometric data were recorded every 2 weeks. Clinical events were registered and HIV viral burden in PBMCs by end-point dilution cultures, CD4+ T cells µL, and TNF-(plasma levels (pg/mL) were evaluated. The efficacy of thalidomide was defined as weight gain or no progression of wasting. Between June 1992 and May 1994, 28 patients (26 men and 2 women) were randomly allocated to receive thalidomide (n = 14). Both groups were comparable in their baseline status. Therapeutic failure occurred in 10 of 14 patients from the placebo group and in 3 of 14 from the thalidomide group ($p = .021$). Weight gain occurred in one patient on placebo and in eight on thalidomide. The Karnofsky index was significantly higher by the end of the study in the thalidomide group ($p = .003$). Mild and transient somnolence and erythematous macular skin lesions were significantly more common in the thalidomide group. CD4+ T cell counts and HIV viral burden in PBMCs did not change in either group. Circulating levels of TNF-(were undetectable throughout the study. Results suggest that thalidomide not only impeded but also reverted the wasting syndrome, preserving the Karnofsky index in patients with advanced HIV disease. Thalidomide, at the dosage used in this study, had no effect on peripheral CD4+ T cells or on HIV viral burden in PBMCs.

Based on this study and other similar reports (Reyes-Terán, Sierra-Madero, Martinez del Cerro, et al., 1996), the Ministry of Health in Mexico approved the use of thalidomide for the treatment of the AIDS wasting syndrome, considering that at the time no better options were available.

There is one sole manufacturer of thalidomide in Mexico, Serral, S.A. de C.V. Raw material is produced in Mexico by Diorchem, a manufacturing plant managed by investigators of the National University of Mexico and the Polytechnical Institute. The drug is not sold in drugstores. It is directly distributed by Serral to infectologists and dermatologists and to the Social Security Institute, the largest public health institution in Mexico.

Thalidomide is supplied in boxes containing fifty 100 mg tablets; the cost of each unit is $38 U.S. The monthly cost of treatment is around $92. This compares favorably to the cost of

megestrol acetate or recombinant human growth hormone (rhGH). It is estimated that total annual sales are in the order of 6,000 units.

The labeling states that thalidomide should not be used in pregnant or fertile women because of the risk of fetal malformations. A pregnancy test must be performed and found negative before treatment is initiated. Contraceptive measures must be used during treatment.

Adverse reactions reported with the use of thalidomide at these high doses have been frequent, but effects have been mild and transient, mostly skin reactions. In the Mexican study, there were two cases of severe skin reaction, requiring discontinuation of the drug in one case. Neuropathy developed in one patient, and the drug was withdrawn.

In conclusion, it can be said that thalidomide seems to delay and reverse the wasting syndrome in patients with advanced HIV disease. The beneficial effects should be investigated in larger clinical trials. It remains to be determined whether thalidomide alone or in combination with rhGH can sustain its effects long enough to significantly alter the clinical course of AIDS, particularly in regard to quality of life and survival in patients with weight loss. Thalidomide can perhaps be used in other wasting diseases, since there have been recent reports of accelerated weight gain when it was used in patients with pulmonary tuberculosis (Tramontana, Utaipat, Molloy, et al., 1995).

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Clinical Pharmacology of Thalidomide

Carol Braun Trapnell, M.D.

Thalidomide was initially developed as a sedative-hypnotic agent in the 1950s. Its use was abruptly halted with the discovery of its potential for causing severe birth defects in children whose mothers were exposed to the drug during pregnancy. In 1965, Sheskin published a report of six lepromatous leprosy patients who had remarkable improvements of the skin manifestations of this disease when each was given thalidomide for sedation (Sheskin, 1965). This report renewed interest in thalidomide, and subsequent research has focused on thalidomide's use as an immunomodulatory agent.

This talk will focus on the clinical pharmacology of thalidomide, including its mechanism of action, absorption, metabolism, drug-drug interactions, and future research directions. The role of thalidomide enantiomers will be discussed. Results of a recently completed clinical research study, evaluating thalidomide's effects on the plasma pharmacokinetics of ethinyl estradiol and norethindrone, will be presented.

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Ethical Issues in the Use of Thalidomide in Fertile Women

Norman Fost, M.D., M.P.H.

I will focus on the potentially competing interests of a woman who might benefit from treatment with thalidomide weighed against the interests of a child who might be born with severe disabling deformities. Because of time limitations, I will not discuss the more intractable question of whether a fetus has any interests in this setting.

Children clearly have interests. They are entitled to protection from physical harm. Child abuse statutes are only one example of widely accepted State action to reduce the risk of harm to children. These interests exist regardless of when the action occurs that can cause the harm. Thus, an action that will likely cause harm months or years after it is taken is still subject to State action. Potential children are entitled to protection.

Parents are not exempted from responsibilities to their own children. Indeed, they have higher responsibilities than others. The State can and does intervene when parents are threatening to act in a way that exposes their children to a high probability of serious harm. Parenthood, or potential parenthood, does not confer immunity against moral judgments or State action to protect children.

Parents, like all patients, are also entitled to a wide range of freedom to choose medical treatments, even when these treatments impose costs and risks on others. Similarly, fertile and pregnant women are generally free to choose medical treatments, as well as substances and behaviors, that expose their future possible children to risks. There is also an especially strong interest in procreative privacy. Neither the interests of children or parents can be absolute. The question, therefore, is how to balance these competing interests.

Some of the variables that affect these balancing judgments will be reviewed. They include (1) the seriousness of the disorder being treated, (2) the likelihood of benefit, (3) the availability of alternatives, (4) the probability and severity of risk to the future child, (5) the availability and burden of reducing the risk to the future possible child, and (6) the importance of the particular pregnancy.

These considerations would lead to different approaches for clinical trials as compared with clinical use after efficacy has been established as well as different approaches for different disorders.

Perspectives From the Public—A Consultation With...

Leo J. Yoder, M.D.

Erythema nodosum leprosum (ENL) is a condition that develops in some patients with Hansen's disease (leprosy), usually after they have been in treatment for a period of time. It is not a reaction to the drugs or treatment but a reaction of the immune system to dead bacteria that remain in the body. Patients with this condition may be acutely ill with fever, painful eruptions in the skin, joint pain, and nerve pain in the extremities. During this reaction, nerve damage to the hands, feet, and eyes can occur. If left untreated, individual episodes will last for several weeks and tend to recur for many months and sometimes for several years. In the years before effective treatment was available, such patients were often suicidal. Even today, treatment options are limited and are primarily the use of drugs such as prednisone or thalidomide.

Prednisone or other corticosteroids are effective in controlling ENL, but the long-term use of prednisone results in side effects such as weight gain, diabetes, hypertension, cataracts, and osteoporosis with collapsed vertebrae of the spine. These side effects can be serious and permanent. In most patients, thalidomide will control ENL completely without the use of prednisone or at much reduced doses. One other drug of some benefit in the treatment of ENL is clofazimine, but it is slow acting and causes pigmentation of the skin.

Thalidomide has some significant side effects. However, these can be avoided if it is used appropriately. The most serious and well-known side effect of thalidomide is severe birth defects when it is taken during early stages of pregnancy. Therefore, thalidomide cannot be given to pregnant women or women of childbearing potential unless pregnancy is excluded and adequate contraceptive measures are instituted before starting the drug. In the United States, the current protocol for treating ENL with thalidomide requires that women of childbearing potential be admitted to the hospital at Carville, Louisiana, to receive the drug. Women without childbearing potential, or men, may receive the drug as outpatients from physicians who have completed required documentation and received approval though the Hansen's disease center at Carville. In most of the world where thalidomide is used to treat ENL, thalidomide use is permitted only in a hospital inpatient setting.

Almost all patients who receive thalidomide will experience some feeling of sedation initially, but they usually adjust to this by taking the medication in the evening. All patients are warned about this effect and are advised to avoid activities that might be hazardous. A painful neuritis is known to occur when thalidomide is used for some other conditions, but this problem has been very rare in patients with Hansen's disease. All patients are advised to report any pain or changes in sensation in the hands or feet. Physicians are also advised of this potential problem, and regular monitoring of nerve function is a part of routine followup. Other side effects of thalidomide noted occasionally are swelling of the feet, constipation, and mild changes in blood counts; these almost never require discontinuing the drug.

Thalidomide has been used for more than 25 years in the United States and other countries for treatment of ENL and has proved very useful for managing this difficult chronic problem without the long-term use of steroids and their associated serious side effects. There have been no known cases of birth defects in the United States resulting from the use of thalidomide for ENL, although some have occurred in other countries where controls and monitoring plans have been inadequate. If used under appropriately supervised and controlled conditions, thalidomide can be used safely, but it is critical that patients and physicians be adequately informed about the risks and side effects that occur in both men and women.

Thalidomide: The Survivor's Perspective

Randolph Warren

The Thalidomide Victims' Association of Canada represents approximately 125 persons born disabled as a consequence of the drug thalidomide. We are the survivors of thalidomide. Our position is clear: We will never accept a world with thalidomide in it. However, we are forced to adopt a position of preferring regulated thalidomide over unrestricted access to the drug (through buyers clubs, smuggling, etc.). We believe that even licensed thalidomide use will mean more thalidomide babies being born or never born.

We believe that the goal for all must be the temporary use of thalidomide, and we strongly encourage research and development of new drugs with the benefits of thalidomide but without the devastating side effects.

We believe that thalidomide should be licensed on a per-medical-condition basis, with each new intended use required to go through a new application process. For example, if thalidomide is licensed for Type II leprosy use, the drug should be made available to only those patients with Type II leprosy. Then, if thalidomide is thought to be beneficial for graft-versus-host disease or another condition, new scientific data based on those conditions would be presented for review and discussion and possibly new licensing. Thalidomide must be carefully restricted, monitored, studied, and ultimately phased out when a new drug is developed to replace it.

We, persons born disabled as a consequence of the drug thalidomide, stand as symbols of what happened before and what may happen again. We will be watching.

If or when thalidomide is licensed, we need to be ever vigilant and to assume responsibility for our actions.

- There must be a guarantee that, when thalidomide is prescribed or distributed, the word "THALIDOMIDE" always will appear beside any brand or trade name reference.

- There must be a guarantee that persons agreeing to take thalidomide will receive clear warnings of all side effects, and therefore know they are making risk-aware choices.

- Ongoing education of the public and professionals on thalidomide must be undertaken and we, thalidomiders, must be involved in establishing those curriculums.

- Research must continue into alternatives to thalidomide.

- The survivors must never be forgotten; someone must be accountable for dealing with any new victims.

To reiterate our position, thalidomiders fear unregulated availability of thalidomide more than

licensing, through which we can expect safeguards and the lowest possible risk of side effects.

Pharmacist's Perspective

William A. Zellmer, M.P.H.

The implications to pharmacists of remarketing thalidomide are discussed from the perspective of this professional's drug-product control and clinical responsibilities. Lessons are drawn from the experience with the control and record-keeping systems in place for isotretinoin (Accutane®). The discussion touches on the growing role of pharmacists in advising patients on the appropriate use of medicines and various factors related to site of pharmacist practice.

Thoughts About Thalidomide: Are We Now and Can We Ever Be Ready for the Mainstreaming of Thalidomide?

Cynthia Pearson

Thalidomide is as potent a symbol as it is a teratogen. It caused one of the worst outbreaks of preventable birth defects the world has ever experienced. Although the number of children damaged by thalidomide may not have been as great as those affected by other agents, such as rubella, the birth defects caused by thalidomide have had a far greater impact. Even in the United States, which was almost spared the thalidomide tragedy because the FDA stood up for women, the painful knowledge brought by thalidomide was powerful enough to change laws and regulations in ways so profound that they affected the life of every person living in this country today.

We now have to consider, given the unique and painful history of thalidomide, whether there is an appropriate way to move forward. The results of clinical trials appear to show two things—that thalidomide is effective for certain conditions associated with life-threatening diseases and that in carefully controlled circumstances it can be used safely by women of childbearing age. However, the logical next step—FDA approval—brings with it the potential for unwise and careless use.

The National Women's Health Network calls for a cautious approach to the provision of thalidomide, one that balances respect for the autonomy and decision-making ability of women, with scrupulous attention paid to provider education and prescribing patterns.

Regulatory Considerations in the Clinical Development of Thalidomide: Safety Monitoring and Investigational Safety Findings

Debra Birnkrant, M.D.

Recently thalidomide has been studied in clinical trials for a variety of serious and life-threatening diseases and also has been used by individual health care providers to treat individual patients who have these disorders. Because of its unapproved status, thalidomide use is deemed investigational and requires authorization by the U.S. Food and Drug Administration (FDA).

Various divisions within the FDA are involved in reviewing clinical trials where thalidomide is under study. For example, the Division of Special Pathogens and Immunologic Drug Products is responsible for reviewing clinical trials of thalidomide for HIV-related aphthous ulcers and HIV wasting syndrome. The Division of Dermatological Drug Products is responsible for reviewing studies of thalidomide for rare dermatological disorders, including erythema nodosum leprosum. Similarly, the Division of Oncologic Drug Products reviews thalidomide trials as they pertain to cancer indications.

Although these indications are diverse, there are common regulatory considerations in the review of thalidomide. The main consideration is safety monitoring. To address safety monitoring for all patients and develop a regulatory accounting of patients who have received thalidomide, the FDA formed a Thalidomide Working Group. The Group has developed a consent form and a patient education brochure to inform both patients and their health care providers about using thalidomide safely.

Both documents contain information about contraception and pregnancy testing based on the window of susceptibility, days 21 to 36 post-conception, when unborn children may be most susceptible to the known teratogenic effects of thalidomide. Other side effects of thalidomide are also described, including sedation, neuropathy, and neutropenia. The consent form and patient brochure advise patients to contact their health care providers if they develop side effects or if women of childbearing potential miss a menstrual cycle. Both documents also contain warnings about sharing medication.

The FDA has also developed a database of individual patients to track regulatory documentation and assess safety-related trends in an aggregated format.

Thalidomide Neuropathy

Herbert H. Schaumburg, M.D.

Sensory peripheral neuropathy appeared, in isolated instances in 1958-59, soon after the introduction of thalidomide (Thd) and reached near epidemic levels in 1960-61. Most initial instances were in healthy persons consuming 50-200 mg daily for sedation; subsequent reports describe a similar neuropathy in patients with dermatologic and rheumatologic conditions. The incidence is not known. Initial symptoms of paresthesias and numbness in the feet appeared within 2-10 months. Robust dose-effect and dose-duration relationships have not been established. Recent carefully monitored studies suggest a correlation of cumulative dose, symptomatology, and electrophysiological changes. Some individuals clearly have had greater doses for longer duration without symptoms; this was claimed as support for a metabolic predisposition in susceptible persons, but studies of genetic differences in drug metabolism have failed to support this notion. Paresthesias, often painful and distressing, spread up the lower limb to the knee and then involve the hands within 2 months of onset, in most reports. Cramps in the legs are common, and a few individuals have developed mild proximal lower limb weakness. Tendon reflexes are often unaffected in mild cases; patella reflexes are occasionally increased. All sensory modalities are impaired to an equal degree. Recovery is variable and initially seems unusually poor for a toxic neuropathy; about one-half of severely involved patients in the early studies reported persistent painful paresthesias 1 year later.

Patients in the earlier reports frequently continued to receive treatment well after the onset of sensory symptoms, and this may account for the poor recovery rate. Poor recovery in this sensory neuropathy likely reflects, in part, distal degeneration of central axonal projections of affected dorsal root ganglion cells. Patients in more recent prospective studies, who ceased medication following the onset of symptoms or who were asymptomatic but displayed diminishing amplitude of sensory nerve action potentials (subclinical neuropathy), have made a satisfactory recovery. Electrodiagnostic studies have consistently displayed loss or diminution of sural nerve and other sensory action potentials within only minor abnormalities of motor nerve conduction. There are increased latencies of somatosensory evoked potentials from the lower limbs, a possible correlate of dorsal column degeneration in the spinal cord. Nerve biopsies, during intoxication, display Wallerian-like degeneration and, after recovery, fiber loss; post mortem studies have disclosed sensory nerve fiber loss, loss of dorsal root ganglion cells, and fiber loss in the dorsal columns of the spinal cord.

Thd neuropathy is no longer a serious problem; rheumatologists, dermatologists, and immunologists are now attuned to the early signs and use sensory nerve conduction studies as a monitor for early subclinical detection. It is suggested that Thd be used only for disabling conditions and only after other therapies have failed; furthermore, doctors who prescribe Thd should have expertise in its use and the resources to detect subclinical or preexisting neuropathy.

Peripheral Neuropathy and Exposure to Thalidomide

Colin Crawford, M.R.C.P., D.P.M.&H.

Thalidomide neuropathy is a very serious complication and can lead to very severe and irreversible sensory loss. This neuropathy was detected when the drug was used as a sedative in Germany, the United Kingdom (UK), and Sweden by clinical neurological examination, supplemented in some cases by sural nerve biopsy and electrophysiological studies, especially sensory nerve action potentials (SNAPs). In one study, sensory loss was found to be permanent in half the patients even several years after stopping the drug.

While the teratogenic effects of the drug can be avoided, everyone who is given the drug runs the risk of developing a neuropathy because there is no minimum safe dose and no evidence that this side effect is due to a hypersensitivity. Since 1965, thalidomide has been used in the management of erythema nodosum leprosum (ENL), a complication of lepromatous leprosy. High doses of the drug have been used for long periods, yet thalidomide neuropathy has not been reported. In contrast, in non-leprosy disorders, the frequency of thalidomide neuropathy is at least 21 percent, if SNAPs are recorded to detect subclinical neuropathy. In the literature, there are few descriptions of the clinical neurological signs in a patient with ENL, because the current classification of leprosy is based on the cutaneous manifestations rather than the neurological findings. There are no reports of SNAPs being recorded in leprosy patients, either before or during treatment with thalidomide.

A symmetrical loss of sensation in the limbs occurs in the late stage of lepromatous leprosy. Sensory loss in patients with ENL, which is associated with a low percentage of viable bacteria, is by no means invariable and in a personal series was present in only 4 of 14 patients. Thus, the use of thalidomide may inflict intractable sensory loss on a leprosy patient that would not have developed as a result of the disease. Where there is sensory loss as a result of the disease, it may be difficult to distinguish from thalidomide neuropathy, especially since, in both, the sensory loss may be confined to superficial modalities. Absence of reflexes is not a reliable sign of thalidomide neuropathy. Distinctive features of thalidomide neuropathy include burning pain in the feet; cramp-like pains in the calf; and, in the later stages, muscular weakness confined to the proximal muscles of the limbs. Nevertheless, the preliminary clinical neurological examination, before thalidomide is started, is essential. Any new signs must be assumed to be due to the drug, especially as sensory loss in lepromatous leprosy develops insidiously.

Recently introduced guidelines for the use of thalidomide by the UK Committee for the Safety of Medicines warn patients to stop the drug immediately if sensory disturbances occur. It also recommended that SNAPs be recorded, both before treatment has started and after each 10-g increment in total dose, or at 6-month intervals. A fall of $\geq$40 percent from the baseline score necessitates stopping the drug. This measure appears to offer the best chance of recovery.

From the evidence available, thalidomide neuropathy has not been excluded in patients given the drug. Moreover, in most accounts concerning the management of ENL in standard medical textbooks, thalidomide neuropathy is not even listed as a side effect. If the UK

guidelines are to be adopted, leprosy patients will need to be warned about the dangers of thalidomide neuropathy. It is difficult to see how the guidelines could be applied to patients with ENL, because even where there is no sensory loss due to the disease, subjective sensory symptoms are common. SNAPS may be altered because of the underlying disease, making detection of thalidomide neuropathy very difficult.

Neurological Testing of Primates

Tucker A. Patterson, Ph.D., W.L. Zielinski, J.C. Reepmeyer, J. Nickols, and W. Slikker, Jr.

Thalidomide (THAL) is currently being evaluated for its therapeutic potential in AIDS and AIDS-related conditions, as well as other serious diseases, such as graft-versus-host disease and erythema nodosum leprosum. THAL has been reported to produce a painful, dose-limiting peripheral neuropathy in patients after chronic administration and alterations in cell-surface markers.

The present study was designed to determine whether THAL could produce end points that may indicate toxicity or the onset of peripheral neuropathy in the healthy adult male rhesus monkey. The end points that were assessed included clinical chemistries and hematologies, nerve conduction measurements, histological analysis, lymphocyte surface markers, and operant behavior. Rhesus monkeys were orally dosed once a day with either 0, 10, or 100 mg/kg THAL (N = 5/group) for 18 weeks using a buffered corn syrup (pH = 5)/biscuit vehicle. Oral dosing with 10 mg/kg/day of THAL produced peak plasma concentrations of 3 to 3.5 g/mL approximately 4 to 6 hours after administration. The plasma levels in these animals remained relatively constant during the 24-hour period and corresponded to the plasma levels of THAL observed clinically (1 g/mL). The high-dose group (100 mg/kg/day) reached peak plasma concentrations of approximately 15 g/mL THAL 6 hours after dosing. The plasma levels remained remarkably high throughout the 24-hour dosing interval (5 to 10 g/mL at 24 hours). In the nerve conduction measurements, there was a trend toward prolongation of the F-wave in both the low- and high-dose groups. This was especially evident after 17 weeks of dosing with a 5 and 12 percent increase in time (ms) for the low- and high-dose animals, respectively. In summary, no overt signs of sedation or toxicity were observed in rhesus monkeys administered doses of THAL that are equivalent to or greater than those typically encountered therapeutically. Additional end points, including operant behavior, cell-surface markers, and histology are currently being analyzed.

Monitoring for Peripheral Neuropathy

Mary K. Floeter, M.D., Ph.D.

Peripheral neuropathy is a common side effect of thalidomide that can be severe and irreversible. Development of peripheral neuropathy may be an indication for discontinuation or reduction of the dosage of thalidomide, and physicians who prescribe thalidomide should monitor patients for this side effect. There are three components to assessment of peripheral neuropathy: (1) patient self-monitoring for typical symptoms, including painful paraesthesias or sensory loss in the feet, and muscle cramps; (2) serial neurological examinations assessing strength, sensation, and reflexes; and (3) physiologic studies such as nerve conduction studies, evoked potentials, and quantitative sensory testing. Measures that assess sensory function are most important, because thalidomide damages large-diameter sensory fibers more than smaller sensory and motor axons (Fullerton, O'Sullivan, 1968). Among such measures, changes in the amplitude of sensory nerve action potentials (SNAPs) have been the most consistent indicator of abnormalities in studies of patients with thalidomide-induced neuropathy.

The first two components of monitoring—history and exam—can be assessed at every visit. There is a general consensus that physiologic studies should be performed prior to treatment, since pre-existing neuropathy may be associated with a higher incidence of thalidomide-induced neuropathy, but there is less consensus on how often physiologic studies should be repeated. One set of guidelines (Powell, Gardner-Medwin, 1994), based on a retrospective analysis of 63 patients treated with thalidomide (Gardner-Medwin et al., 1994), recommends performing nerve conduction studies that include three SNAPs twice before treatment and, thereafter, at 6 month intervals or after a 10-g increment in dose. These guidelines recommend discontinuation of thalidomide if a patient develops symptoms of neuropathy or if the weighted average of the three SNAP amplitudes falls by 40 percent. In another retrospective analysis of 42 patients (Ochinsky et al., 1994), most who developed peripheral neuropathy first developed symptoms, followed by objective deficits on neurologic exam, and abnormalities of nerve conduction studies. Nerve conduction studies were repeated every 6 months, only when patients developed symptoms. In some patients, who had no objective deficits, thalidomide was continued without subsequent development of objective signs.

The variability in individual measures of SNAP amplitudes is a limitation to their use in monitoring. Variability arises from differences in techniques between laboratories and examiners, as well as from patient differences that alter the detection of the electrical signals, including peripheral edema, skin-thickening, and temperature of the hands and feet. To limit variability, it is advisable for the same examiner to perform the baseline and followup studies and to include measures of several SNAPs on each occasion. It has been suggested that nerve conduction studies may allow detection of subclinical neuropathy (Gardner-Medwin et al., 1994). This claim has not been tested prospectively, but it deserves further evaluation.

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Characterization of Embryopathy Risks

Barbara A. Hill, Ph.D.

Thalidomide was introduced to the German market as Contergan in 1956 by a West German company, Chemie Grunenthal. After 1958, it was marketed in the United Kingdom and other countries as a sleeping aid notable for its prompt action, lack of hangover, and apparent safety. The observation of peripheral neuropathy, associated with long-term thalidomide administration, was the first indication that the compound produces serious adverse effects. This observation was quickly overshadowed when separate reports, generated by McBride in 1961 and Lenz in 1962, demonstrated an association between maternal thalidomide usage and infant limb defects. Substantial evidence accumulated indicating that exposure of the fetus to even a single dose (100 mg) of thalidomide, during the sensitive period (34-50 days post-menstruation), induced a characteristic profile of birth defects. The most readily observed effect of thalidomide exposure was the presence of phocomelia or amelia of the limbs, but this effect was frequently combined with defects of internal organs (i.e., cardiovascular system, duodenum, respiratory system, urogenital tract, and gall bladder).

It has been determined that the type of limb defect (either phocomelia or amelia of arms or legs), as well as the defects of internal organs, was dependent on the time within the sensitive period that the fetus was exposed to thalidomide. An estimated 5,000 to 6,000 infants were reported to have characteristic thalidomide-induced phocomelia, often accompanied by deformities of internal organs, during the time that thalidomide was marketed in Germany and the United Kingdom. Thalidomide was withdrawn from the world market in late 1961, remaining available only for strictly defined research purposes.

During the 35-year period since the initial identification of thalidomide as a teratogen, many attempts have been made to determine the teratogenic mechanism of thalidomide. Unfortunately, the actual mechanism of action of thalidomide embryopathy remains unknown despite the numerous studies conducted over the past three decades. Because of the recent resurgence of the use of thalidomide for a variety of indications, ranging from the treatment of erythema nodosum leprosum (a complication of lepromatous leprosy) to the treatment of aphthous ulcers and wasting associated with HIV infection, there remains an urgent need for understanding the mechanism of teratogenicity induced by thalidomide. A considerable number of hypotheses have been proposed to explain the etiology of thalidomide embryopathy. This presentation will focus on reviewing the leading candidates and discussing their potential merits and pitfalls.

Pregnancy Prevention in Patients Taking Thalidomide

Christine K. Mauck, M.D., M.P.H.

Women taking thalidomide during the "sensitive period" of pregnancy are at risk of having a thalidomide-affected pregnancy. In the absence of contraceptive use, 85 percent of sexually active women of childbearing age become pregnant within 1 year. Only hysterectomy, sustained abstinence, and documented menopause are 100 percent effective in preventing pregnancy. Contraception can reduce the chance of pregnancy by up to 99.9 percent. Efficacy is affected by compliance for many methods, such as oral contraceptives and barriers. Using two methods can improve efficacy. The use of emergency contraception when a woman suspects loss of contraceptive protection (failing to take her pill or to use a barrier, or breakage/slippage of a barrier) can further reduce the likelihood of pregnancy.

If pregnancy is not prevented, it can be diagnosed about 10 days after conception, before the menstrual period is late. The difficulty is knowing when to test and how frequently to test.

After discussions with reproductive toxicologists and obstetrician/gynecologists, the FDA recently proposed to require a negative pregnancy test at baseline, 9-10 days after starting therapy, and every 30 days thereafter. Male thalidomide users should use condoms.

If a woman gets pregnant and has taken thalidomide during the sensitive period, the likelihood of fetal abnormality has been estimated to be 10-50 percent, although estimates are imprecise and a figure of 100 percent also has been cited.

In consultation with her physician, the woman may choose to continue the pregnancy. She may elect to undergo frequent fetal monitoring, although ultrasound cannot detect most defects before 12 weeks and may not pick up some defects at all. There is a 10-15 percent chance that the woman will spontaneously abort, based on miscarriage rates among women who have not taken thalidomide. The effect of thalidomide on the chance of spontaneous abortion is not known. Given the high rate of severe fetal defects among women who take thalidomide during the sensitive period, the woman may elect to undergo an induced abortion, which is very safe if done early.

If thalidomide becomes widely used, it can be expected that pregnancies will be conceived during the sensitive period; some of these will be carried to term, and some infants will be born with thalidomide-related defects. Education of potential users will be very important to minimize the number of affected infants.

How Environmental Effects on Child Health Are Recognized

Robert W. Miller, M.D., Dr.P.H.

Almost all environmental teratogens and carcinogens have first been identified by an astute observer, usually, but not always, a clinician. Thus, in the 1920s, small head size and mental retardation were first noted in newborn infants whose mothers had received therapeutic radiation to the abdomen during pregnancy; in 1941, Gregg, an Australian ophthalmologist, linked cataracts and associated congenital defects to maternal rubella during pregnancy; in 1941, McBride, an Australian, and Lenz, a West German, independently noted that clusters of newborn infants with phocomelia were linked to maternal use of thalidomide early in pregnancy; and, in 1971, Herbst et al. reported that clear-cell adenocarcinoma of the cervix or vagina, a disease of old women, had occurred in four young women in Boston. The next step was to confirm and extend this clinical observation by epidemiologic studies, which implicated the cause to be diethylstilbestrol given early in pregnancy in an effort to prevent miscarriage.

Epidemiologic studies can be retrospective (starting with the disease and looking backward into history for the cause) or prospective (starting with an exposed population and looking forward over time for the occurrence of the disease). It is not enough simply to show an association between a presumed cause and an effect. The finding should be supported by as many of the following as possible: replication by other investigators; a dose-response effect (the larger the dose, the greater the effect); biologic plausibility; induction of the effect by the exposure of experimental animals; excluding the effect of confounding variables, such as cigarette-smoking in a study of other causes of lung cancer; and disappearance of the effect after removal of the cause. Practicing physicians should be encouraged to call attention to unusual occurrences of disease showing some evidence of an environmental effect.

Experience With Accutane

Allen A. Mitchell, M.D., Carla Van Bennekom, M.P.H., and Carol Louik, Sc.D.

In 1982, the vitamin A analog isotretinoin (Accutane®, Roche) was introduced into the United States for the treatment of severe, recalcitrant, cystic acne. Suspicions that it was a human teratogen, noted at the outset, were documented in 1985; approximately 25 to 30 percent of infants exposed in utero had malformations that included craniofacial, heart, and central nervous system defects. In the fall of 1988, the manufacturer introduced a novel and aggressive pregnancy prevention program (PPP). Components included a unique blister package for the medication with prominent warnings, detailed guidelines to physicians, a patient qualification checklist, a patient information brochure, contraceptive information, a free contraception referral program, and an informed consent form. Guidelines instructed physicians to warn patients of the risks, obtain negative pregnancy tests, and delay therapy until the second or third day of the next menstrual period.

Since 1989, we have conducted a survey (supported by the manufacturer) designed to assess physician and patient compliance with the PPP and to identify the rate of pregnancy during therapy and in the month following treatment. Participation in the survey is voluntary; enrollment forms are provided by physicians and in the medication package, and each woman is paid $10 upon enrollment. Women are followed throughout their course of therapy (typically, 5 months) and for 6 months thereafter.

To date, more than 350,000 women have enrolled, with an increase in enrollments observed over time; the mean age of the women is 26 years, and their mean educational level is 2 years of college. Women in the survey, relative to the general U.S. population, were at lower risk for pregnancy, either because they were not sexually active or because they used relatively effective contraception. The vast majority (99 percent) were told of the importance of avoiding pregnancy; compliance with other measures of the PPP, although variable, tended either to remain stable or to improve over time, the latter associated with enhanced educational interventions initiated by the manufacturer. Among 210,009 women with completed followup, pregnancies occurred in 623 while on therapy, for a rate of 7.7/1,000 woman-years; this rate is roughly 7 percent that of the U.S. population. Between 1989 and 1995, the pregnancy rate has declined, from 10.3 to 6.8/1,000 woman-years, respectively. The large majority of pregnancies (68 percent) were electively terminated, and 11 percent resulted in a live birth.

Because enrollment was based on voluntary participation, it is not clear whether the findings from this survey are representative of all women who take Accutane. Evaluation of the effectiveness of this PPP must take into consideration a number of factors that relate to Accutane and the Accutane PPP; these include (1) only one manufacturer involved in the formulation and promulgation of the PPP, (2) prescription of the drug by doctors largely from a single specialty where Accutane is an important part of practice, and (3) a patient population that is well educated. These and other characteristics of this experience make it difficult to predict whether

the Accutane PPP would be similarly effective for other human teratogens.

Preventing Birth Defects Due to Thalidomide Exposure

Cynthia Moore, M.D., Ph.D.

Thalidomide is a powerful human teratogen that causes hypoplastic and aplastic malformations of the limbs as well as other serious birth defects. In the late 1950s and early 1960s, as many as 10,000 children worldwide were identified with thalidomide embryopathy. In countries where thalidomide is currently available, affected infants are still being born. If thalidomide is made available in the United States, it will be used by women of childbearing potential, and babies will be born with thalidomide embryopathy. Therefore, it would be prudent to have specific recommendations in place, before the drug is marketed, to help minimize the number of serious birth defects caused by thalidomide.

On March 26, 1997, CDC convened an open workshop entitled "Preventing Birth Defects Due to Thalidomide Exposure" to discuss ways to limit fetal exposure to thalidomide should the drug be approved for prescription use by the FDA. The workshop was attended by individuals from Federal and State agencies, academia, the pharmaceutical industry, managed care organizations, professional practice organizations, and others who have expertise or interest in the area of birth defects prevention.

All suggestions made by participants were considered by the CDC in the development of the following *DRAFT* recommendations to prevent birth defects due to thalidomide exposure:

- Ensure that the patient is a suitable candidate for thalidomide use.

- Ensure that all patients are counseled about the teratogenicity of thalidomide and female patients of childbearing potential are counseled about effective contraceptive methods.

- Ensure that thalidomide is packaged and dispensed in a manner which minimizes inappropriate or inadvertent use.

- Ensure that prescribing health care providers and pharmacists have adequate knowledge about thalidomide and guidance in its use.

- Ensure that female patients of childbearing potential are adequately monitored during thalidomide use to reduce the risk of fetal exposure.

- The presentation by CDC at the FDA hearing on September 4, 1997, will expand and explicate these overall recommendations.

The goal of minimizing the number of birth defects that occur because of thalidomide exposure will require a cooperative effort from all persons involved with the treatment. This joint effort should include the patient, the prescribing health care provider, other appropriate

health care providers, the pharmacist, the pharmaceutical company, professional societies, and regulators. The responsibilities, as well as the burdens, for following the recommendations are shared by all parties.

Clinical Ethical Considerations in the Use of Thalidomide: A Practitioner's Perspective

Gail J. Povar M.D., M.P.H., F.A.C.P.

Thalidomide has undergone a sort of pharmacotherapeutic rehabilitation since it was disapproved by the FDA decades ago. Although the risks of teratogenicity persist, thalidomide's attraction lies in its apparent effectiveness in treatment of a wide variety of immune-mediated disorders, from aphthous stomatitis to graft-versus-host disease. Yet, perhaps because of its grisly past, there seems to be particular concern about the ethical dimensions of reintroducing this drug in the United States for general use.

For the most part, however, thalidomide poses no more—and no less—a challenge to the practitioner than any other drug with substantial promise and potential toxic effects. In every instance, the clinician must abide by central tenets of medical ethics: to do good, to avoid (unnecessary) harm, and to respect the patient's values and choices. Doing good and avoiding harm entails recommending treatment that is indicated on the basis of ample and respectable research and for which the toxicity profile is proportionate and acceptable to the patient. Like Accutane®, another widely used teratogen, thalidomide will likely spark disagreements both within the medical community and between medicine and the public about what limits, if any, to impose on use in fertile women. In addition, because of its exciting potential in the amelioration of serious illness, thalidomide may tempt clinicians to go beyond well-documented indications to more experimental applications. The ethical requirements then extend beyond the informed consent and risk-benefit assessments of standard medical practice to those of clinical research.

Risk Management—Educational, Advertising, and Marketing Efforts: Industry Perspectives

Bruce A. Williams

The submission of an NDA (New Drug Application) for the use of thalidomide in any clinical condition imposes a unique and sobering challenge on the manufacturer/sponsor. Celgene has undertaken this challenge and submitted an NDA for the use of thalidomide to treat erythema nodosum leprosum, a severe inflammatory condition associated with leprosy, in December 1996. A supplemental NDA for the treatment of wasting associated with AIDS is being prepared. In parallel, we have consulted with a wide range of public health officials, regulatory and scientific agencies, physicians, pharmacists, patient advocates, women's health advocates, and adult victims of the thalidomide tragedy of the 1950s and 1960s. Our primary objective is to develop patient and professional educational programs, counseling, prescribing guidelines, distribution controls, and followup surveillance to prevent fetal exposure to thalidomide.

The Celgene Thalidomide Fetal Exposure Prevention Program has been designed with the knowledge that other human teratogens (e.g., Accutane) are in routine clinical use in the United States. Programs have been designed to "prevent pregnancy" in women taking these drugs. In addition, other drugs with severe side effects (e.g., Clozaril) are supported by restrictive distribution systems designed to minimize the associated risks. The Celgene program builds on these efforts and, more importantly, builds in unique elements, creating a system with a high degree of control as well as continuous feedback and improvement.

The Celgene Thalidomide Fetal Exposure Prevention Program will include education on the risks related to thalidomide therapy, education, and counseling on effective contraception, pregnancy testing protocols, informed consent to be signed by all patients and their doctors, a confidential survey to be completed by all patients on initiating therapy, during therapy, and following the completion of therapy, and a distribution system designed to ensure that only registered pharmacies and physicians complying with the program can prescribe and dispense the drug.

Importantly, the program is designed to minimize intrusiveness and barriers to appropriate use. Clinical research has demonstrated in ENL, and suggested in a variety of other potential indications, that thalidomide can offer significant therapeutic benefits to patients who suffer greatly from diseases for which either there are currently no effective therapies or these therapies have limited effectiveness. The Celgene Thalidomide Fetal Exposure Prevention Program is a response to both the need to prevent a new thalidomide tragedy and the humane need to ensure that those who need this therapy can have appropriate access to it.

Thalidomide: Bioethical and Legal Issues—Industry's Perspective on Present and Future Needs

Peter Andrulis, Ph.D.

Thalidomide, a drug unique in its risk, and now apparently unique in its promise, is showing itself to be unique in its challenges.

While all who now work, or will work, with thalidomide, need to understand the challenges they face in managing its safe and effective use, the responsibility assumed by the pharmaceutical company that develops, markets, and sells the drug is virtually unprecedented.

Some experiences and insights acquired over 10 years of working with thalidomide will be shared; these include the conflicting and complementary forces at work in responding to compassionate use requests as well as in rendering market-based decisions.

In 1987, Andrulis Pharmaceuticals Corporation became the first firm to manufacture thalidomide, the first to commence clinical trials, and, through the sponsorship of the Division of AIDS at the National Institute of Allergy and Infectious Diseases, the first to report on its striking effectiveness in a Phase II/III trial against aphthous ulcers, an AIDS-related condition that also afflicts HIV-negative immunocompromised patients. Andrulis also has demonstrated the anecdotal efficacy of thalidomide in pilot Phase I/II trials against AIDS-associated Kaposi's sarcoma and prurigo nodularis, Crohn's disease, brain cancers, and is studying its efficiency against multiple sclerosis.

Legal Perspective

Frank C. Woodside III, M.D., J.D.

Despite clear evidence that thalidomide causes certain birth defects, it is now under consideration as a treatment for aphthous ulcers in AIDS patients, erythema nodosum leprosum seen in leprosy patients, and a number of other angiogenic diseases including cancer, macular degeneration, and rheumatoid arthritis.

With these potential benefits, however, it is clear that risks that can be avoided should not prevent the use of thalidomide in controlled situations. Certain precautions must be taken. First, there must be extensive testing, not only to identify all the potential risks, but also to confirm that the drug provides all of the claimed benefits. Standard testing would properly identify all of the risks and benefits.

Conducting the appropriate toxicological and clinical studies, and ensuring that the risks outweigh the benefits, would also assist in alleviating the problem of any future product liability claims. Typically, in tort law, a drug like thalidomide would be subject to strict liability and be considered defective and unreasonably dangerous if a defect in the design of the drug made it unsafe for its intended use. Despite its benefits, the unborn children of pregnant thalidomide users would be subject to significant risks. Tort law, however, creates an exception for products that satisfy a risk-benefit analysis. Thus, the availability and marketing of thalidomide is justified, notwithstanding the risks, if its known or perceived benefits outweigh its known or perceived risks.

If thalidomide comes to market, manufacturers, to avoid potential liability, would also be duty bound to warn consumers. A useful paradigm can be found in the marketing and selling of Isotretinoin (commercially known as Accutane®). Accutane, an anti-acne drug, was known to cause malformations in the offspring of animals that were given the drug during pregnancy. Thus, the marketing and sale of Accutane were accompanied by thorough and extensive warnings. Warnings were contained in the packaging, directed to physicians and pharmacists, and finally forwarded to patients directly. Furthermore, the FDA advised blood banks not to accept as donors those individuals who were taking or recently had taken the drug. The manufacturer also suggested pregnancy tests for female patients before they began any therapy associated with the drug. As a result, there are few reported lawsuits involving Accutane and birth defects. When faced with similar risks associated with thalidomide, the manufacturers should certainly pursue a similar course of action.

Thalidomide Revisited—The Nightmare To Come

Thomas H. Bleakley, J.D.

In 1959, thalidomide was being marketed as a safe sedative in 48 countries; doctors had already reported that 12 West German children with truncated limbs had been born to women using the drug. By the time thalidomide was taken off the worldwide market in 1962, 10,000 to 12,000 babies had been born with missing or malformed limbs, facial deformities, and defective organs. About half of these children died in infancy. Only a handful of children were affected in the United States. In the aftermath, the manufacturers of this disastrous drug resisted the imposition of liability for nearly a decade. Finally, they entered into a compensation scheme that gave each child a mere pittance, based on the number of limbs they were missing.

Since that time, America has changed. We are a more complex culture. What has changed most dramatically is the expectation of justice. We have developed a growing appetite for human rights that epitomizes the great American dream—justice for all. With that dream in mind, this plea for justice for these unborn children is made. The potential realization of this expectation has been drastically curtailed over the past decade as a result of so-called “tort reform” measures that sharply limit the ability of injured persons to recover compensation.

In Michigan, for example, the law after tort reform holds that FDA approval of a drug means that the drug is safe; the user is left without a legal remedy for harm caused by the drug unless it can be determined that FDA approval was obtained by fraud. Similarly, in most States the counterfeit lawsuit crisis, engineered by corporate America, would leave a child damaged by thalidomide without an adequate remedy at law.

It must not be forgotten that the major impetus driving the present inquiry is the profit motive of the corporation seeking this drug's approval, and it is likely, even with optimal safeguards, that children will be damaged by the drug. Consider the following scenario: 5 years from today, a child exposed inadvertently to thalidomide is born without arms and legs. A lawsuit is filed and eventually dismissed as a result of tort reform measures. The child is condemned to a lifetime of welfare and second-class citizenship, an object of curiosity and ridicule. Such children must be allowed a semblance of dignity by ensuring that those who would compromise our constitutional rights do not throw the babies out with the bath water. Failure to protect these children, by preventing the occurrence of this event, is to perform an end run around sensible benefit-versus-risk assessment. Failing to do so would carry the doctrine of caveat emptor, let the buyer beware, to an unjust and unfair end point.

Thalidomide: A Molecular Template for Drug Discovery

David Stirling, Ph.D.

Thalidomide has a very simple chemical structure with a molecular weight of 258. Despite this apparent chemical simplicity, it can catalyze a number of powerful biological reactions when administered as an oral medication. These activities include sedation, teratogenicity, inhibition of tumor necrosis factor-alpha (TNF-alpha) synthesis, and possibly inhibition of angiogenesis. A program was developed to design novel therapeutics that would accentuate the positive actions of the drug, for example, inhibition of TNF-alpha synthesis, while minimizing or eliminating negative activities such as teratogenicity.

A large number of compounds have been designed, synthesized, and tested for their ability to inhibit the proinflammatory cytokine TNF-alpha. In cellular-based assay systems, new compounds have exhibited potencies more then 10,000 times the potency observed with thalidomide. The overall safety and efficacy profile of these new chemical entities will be discussed. The first representative of these new compounds will enter initial clinical testing later this year.

Pharmacology, Pharmacokinetics, and Teratology of Thalidomide and Analogues

Edward J. Shannon, Ph.D.

Thalidomide (α-phthalimide-glutarimide) is very effective in alleviating erythema nodosum leprosum in leprosy patients and aphthous ulcers in AIDS patients. The cause of these inflammatory diseases and the mechanism by which thalidomide attenuates them is unknown. It has been suggested that modulation of the immune response plays an important role. We found that thalidomide exerts immunomodulatory activity in several bioassays.

In vivo, thalidomide suppresses an IgM spleen cell plaque forming cell response in mice injected intravenously with sheep erythrocytes. In vivo, it inhibits the synthesis of tumor necrosis factor-alpha (TNF-ατ when human mononuclear cells are stimulated with lipopolysaccharide, and also enhances the synthesis of IL-2 when human mononuclear cells are stimulated with concanavalin A. We used these bioassays to compare the activity of 15 analogs of thalidomide with thalidomide itself. Thalidomide was used in concentrations that are equal to those attained therapeutically in humans. The analogs were equal in molarity or weight to thalidomide. Eight of the compounds were derivatives of the glutarimide moiety of thalidomide, and the others were phthalimide or derivatives of the phthalimide moiety.

N-hydroxyphthalimide, a simple derivative of phthalimide, was more effective than thalidomide and was also the most effective of the compounds assayed in suppressing the IgM plaque and TNF-α responses. In contrast to thalidomide, it did not enhance the synthesis of IL-2; it significantly suppressed it.

Structure-activity relationships of thalidomide and analogs of thalidomide are being studied in several laboratories. In one laboratory, analogs of thalidomide are being compared with thalidomide for their ability to enhance the synthesis of TNF-α, whereas, in another laboratory, analogs are being compared with thalidomide for their ability to suppress the synthesis of TNF-α. The ability of thalidomide to be antagonistic or agonistic to the synthesis of TNF-α does not help to validate the role of a single assay in studying structure-activity relationships. However, the use of two or more assays to study structure-activity relationships seems to complicate the screening process. Regardless of the assay or assays used, it is hoped that an analog of thalidomide or another class of compounds will be found that will overcome the major disadvantages of thalidomide, i.e., teratogenesis and neuritis.

Thalidomide for the Treatment of Prurigo Nodularis of HIV-Infected Patients

Toby A. Maurer, M.D., A. Poncelet, J. Badger, K. Legarre, M. Burney, J. Ng, and T.G. Berger

Objective

To determine the safety and efficacy of thalidomide for the treatment of prurigo nodularis (severely itchy skin nodules) in HIV-infected patients.

Methods

HIV-infected patients with prurigo nodularis refractory to treatment with high-potency steroids, ultraviolet light, and antihistamines were enrolled in a randomized clinical study. All patients received thalidomide at 100 mg per day (Andrulis Pharmaceuticals). After 1 month, patients were randomized to continue at this dose or to receive 200 mg per day. Patients were monitored for reduction of itch, both subjectively and objectively, on a monthly basis. Patients were also followed for the development of peripheral neuropathies. They were examined clinically by a neurologist and were given nerve conduction tests at baseline every 3 months and if new symptoms developed. When peripheral neuropathies developed, patients had the option of decreasing their dose of thalidomide to as little as 50 mg per day.

Results

We present the results of 14 patients who were enrolled in this study over a 2-year period. After the first visit, one patient died, and two patients were lost to followup. Two patients could not receive thalidomide, one because of severe peripheral neuropathy at baseline and the other because she refused birth control. These two patients were used as controls. Twelve of fourteen patients were African American; all patients were photosensitive. Of the nine patients followed long term, four developed peripheral neuropathies that resolved with a reduction in thalidomide dose. Itch was reduced by 25 percent after the first month of treatment and by 50 percent after the first 3 months of treatment. Nodules and plaques were reduced by 50 percent, but not until after an average of 3 to 4 months of treatment. Because of peripheral neuropathies, the dose of the drug was often reduced to 50 mg per day, which was enough to sustain control of itching. The most common side effects were weight gain and constipation. No drug rashes were noted over a 2-year period.

Conclusions

Thalidomide appears to be an alternative for prurigo nodularis in HIV-infected patients. Relief of itching is an early event. Monitoring for peripheral neuropathies is essential. Reducing the dose of thalidomide may result in reduction or resolution of the neuropathy while sustaining the anti-pruritic effect. The side effects of this drug seem tolerable in this setting. Thalidomide should be considered in the treatment of other pruritic diseases associated with HIV infection, the prevalence of which has been reported to be 50 percent of all HIV dermatologic manifestations.

Erythema Nodosum Leprosum

Thomas H. Rea, Jr., M.D.

Erythema nodosum leprosum (ENL), or Jopling's Type II reaction, occurs most often in lepromatous patients, in up to 75 percent of cases, and is a major source of morbidity in these individuals. ENL is not ordinary erythema nodosum occurring in leprosy; it is a leprosy-specific response that has some features in common with ordinary erythema nodosum. Also, ENL is not a complication of therapy, occurring before, during, or after treatment. Clinically, this reaction is characterized by crops of painful and tender, bright pink, dermal and subcutaneous nodules arising in clinically normal skin in association with fever, anorexia, and malaise. Because of the other organs involved, arthralgias and arthritis are more common in ENL than are neuritis, adenitis, orchitis/epididymitis, or iritis, but each may rarely be the initial structure affected. Involvement of both upper and lower extremities is the rule, and facial lesions occur in one-half of the patients. A neutrophic leukocytosis is usual, and occasionally leukemoid in degree. Severe episodes can be associated with an abrupt fall in hematocrit, up to 5 g/100 mL. The response to thalidomide may be dramatic, perhaps qualifying as a diagnostic criterion. ENL can be precipitated by pregnancy or pyogenic infections. The course of ENL, treated or untreated, ranges from sporadic and ephemeral to frequent and persistent, lasting a matter of years.

The usual histologic features are small foamy granulomas in the dermis and subcutaneous tissue (lobular panniculitis) with increased numbers of lymphocytes and a variable number of neutrophils. Acid-fast bacilli are usually found with ease but may be rare in late presentations (after 2 years of treatment).

When ENL is active, morbidity is caused by general toxicity or acute inflammation in involved tissues, such as nerves and joints, and when ENL is in remission, silent neuropathy results in loss of protective pain sensation.

Thalidomide therapy offers complete control of ENL in 90 percent of patients, with few side effects. In contrast, corticosteroids are associated with less effective control and their own substantial morbidity. Clofazimine may be only a steroid-sparing agent. Drugs of unproven value but continued interest include pentoxifylline and cyclosporin.

Putatively, ENL is immunologically driven, but no proposed mechanism is satisfactory, and the database is not consistent. An immune complex hypothesis has many adherents but is confounded by lesional signs of cellular immunity such as keratinocyte DR framework antigen, increased cells hybridizing for IFN(-mRNA, and excess of IL-2 staining cells as well as by the precipitation of ENL by the administration of rhIFN(g. With the onset of ENL, the infiltrating T cells switch from a $CD8^+$ to a $CD4^+$ predominance, but the RT-PCR cytokine profile remains Type 2. Following the lead of thalidomide responsiveness, tumor necrosis factor-alpha may be ENL's major mediating cytokine, but a specific immunologic pathway has not been identified.

Thalidomide for Behçet's Disease and Complex Aphthosis

Alan B. Fleischer, Jr., M.D., and Joseph L. Jorizzo, M.D.

Behçet's disease is a rare, chronic relapsing inflammatory systemic disease of unknown etiology, characterized by inflammation of the eyes and ulcers (aphthae) of the mouth and genitals. Most commonly, patients present with oral aphthae in association with genital aphthae and possible systemic involvement of the eye, skin, joints, gastrointestinal tract, or brain. Jorizzo and colleagues described complex aphthosis, a forme fruste or limited form of Behçet's disease. Patients with complex aphthosis present with oral and genital aphthae or almost constant, multiple (more than three) oral aphthae but no systemic signs or symptoms. Patients with complex aphthosis develop additional manifestations of Behçet's disease, but many may continue in their more limited extent of illness. Because of the difficulty in precise diagnosis, Behçet's disease and complex aphthosis are diagnosed by means of published criteria. Both Behçet's disease and complex aphthosis produce much suffering, detracting from a patient's quality of life.

Although therapy is available, most treatments for mucocutaneous disease have marginal benefit. Anecdotally, individual case reports and small case series have suggested that thalidomide is the treatment of choice for mucocutaneous disease. Aphthae recalcitrant to all other forms of treatment have rapidly healed in approximately 80 percent of reported patients. Jorizzo initially used thalidomide in doses up to 200 mg per day, but he and others found that 100 mg per day is sufficient to heal most new lesions within 1 week. The clinical sense is that thalidomide will prevent the emergence of new lesions; hence, thalidomide may represent good maintenance therapy. To date, there has not been a randomized, controlled trial of thalidomide for this condition. Jacobson and colleagues studied a possibly related condition, aphthae in patients with HIV infection. In this randomized, double-blind placebo-controlled trial, thalidomide was highly effective. Unfortunately, results from this latter trial may not be generalizable, since many features of HIV-associated aphthae differ from those seen in patients with Behçet's disease and complex aphthosis.

Thalidomide in Pyoderma Gangrenosum

Mervyn L. Elgart, M.D.

Four patients with pyoderma gangrenosum were unresponsive to prednisone, cyclosporin, colchicine, cytoxan, and dapsone. In an open, nonblinded study, all four were treated with thalidomide, with doses up to 200 mg per day. Two cleared completely, on doses of 100 mg per day, and remained clear for a 1-year followup after thalidomide was discontinued. One of the others cleared partially (two of three lesions clear, one remaining). The other had to discontinue medication because of side effects, which included paresthesias in her legs and vaginal bleeding.

Both of the successful patients cleared at a dose of 100 mg per day, and did so in less than 6 months. One of the successful patients was HIV-positive. He had less than 100 CD4 cells at the time of treatment. He had been on AZT, prednisone, fluconazole, acyclovir, clarithromycin, trimethoprim/sulfamethoxazole, ketolac, naproxen, and Percocet. The CD4 count did not change significantly during therapy. The HIV RNA was not evaluated. The patient who cleared partially after 2 years has a history of discoid lupus erythematosus as well as pyoderma gangrenosum.

Side effects have included temporary tingling in one patient and permanent paresthesias in another. The female patients were protected from pregnancy by abstinence in one case, or by a husband's vasectomy and continued use of condoms in the other. There were no instances of thyroid abnormalities or other blood changes.

Discoid and Systemic Lupus Erythematosus

John H. Klippel, M.D.

Discoid lupus erythematosus (DLE) is a chronic, disfiguring cutaneous lesion characterized by plaques with hyperpigmentation at the expanding border and atrophic scarring in the central portion of the lesion. The light-exposed areas of the skin (e.g., face, ears, scalp, V-region of the neck, and extensor surfaces of the forearm) are most commonly involved. DLE may occur in the absence of systemic illness or be a manifestation of systemic lupus erythematosus. The pathology of DLE reveals hyperkeratosis, follicular plugging, and a dense infiltration of lymphocytes; an interaction between gamma/delta T cells and heat shock protein is thought to play an important role in damage to the basal layer. Both anti-inflammatory and immunosuppressive therapies are used, including topical and intralesional corticosteroids, antimalarials, azathioprine, and retinoids.

Although improvement with conventional treatment is observed in most patients, approximately 10 to 20 percent of DLE patients are resistant to treatment and develop progressive scarring. Several studies have documented that thalidomide (100-400 mg/d) may have a role in the management of treatment-resistant DLE (Rubio, Gonzalez, 1975; Knop, Bansmann, Happle, et al., 1983; Atra, Sato, 1993). Within 2 weeks of beginning therapy, 90 percent of patients were reported to have major improvement in skin lesions. Discontinuation of thalidomide was associated with relapse of DLE in all patients. The role of thalidomide in systemic lupus erythematosus has not been well studied, although there is a suggestion that it may be valuable in the treatment of lupus arthritis and as a corticosteroid sparing agent (Bessis, Guillot, Monpont, et al., 1992; Atra, Sato, 1993).

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A Pilot Study of Thalidomide for Primary Sjögren's Syndrome

Stanley R. Pillemer, M.D.

Sjögren's syndrome (SS) is a systemic autoimmune disease that predominantly affects women. SS is characterized by lymphocytic infiltration of lacrimal and salivary glands leading to secretory function loss and the symptoms of dry eyes and dry mouth. After bone marrow transplantation, patients with chronic graft-versus-host disease often develop symptoms of oral dryness and salivary gland lymphocytic infiltrates indistinguishable from SS.

Thalidomide has not been studied as a treatment for SS, but pilot studies suggest that it may be beneficial in the treatment of a number of autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, and various skin disorders, as well as in the treatment of chronic graft-versus-host disease. Major adverse effects of thalidomide include teratogenicity, neuropathy, and sedation. The study is a 12-week randomized, double-blinded, pilot clinical trial designed to screen for potential efficacy and to evaluate the safety and potential adverse effects of thalidomide compared with placebo in patients with primary SS.

Treatment of Rheumatoid Arthritis With Thalidomide

Sicy Lee, M.D., Jeffrey Klausner, Stephen Oliver, Gilla Kaplan, Eillen McCullagh, and Steven Abramson

There is compelling evidence that tumor necrosis factor-alpha (TNF-alpha) plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA), and recent studies have demonstrated that inhibition of TNF-alpha with monoclonal antibodies to TNF-alpha resulted in significant clinical improvement of patients with active RA. The purpose of this study was to investigate whether thalidomide, an inhibitor of TNF-alpha, would be efficacious in the treatment of RA. The protocol anticipated 50 patients with active RA to participate in a 16-week randomized, double-blind, placebo-controlled pilot study. However, the study was terminated after treatment of 12 patients because of an unacceptably high rate of adverse events in the thalidomide group. Of the 12 patients, 4 (75 percent female) received placebo, and 8 (88 percent female) received thalidomide. The mean ages were 51 and 59, and mean durations of RA were 6.9 and 16.3 years in the placebo and thalidomide groups, respectively. In the placebo group, 2 patients withdrew because of lack of response at weeks 8 and 12. In the thalidomide group, only 1 patient completed the 16-week study. The reasons for early withdrawal in the thalidomide-treated group were as follows: 1/7 at week 8 due to peripheral neuropathy; 3/7 due to tremors at weeks 2, 4, and 6; 2/7 due to rash at weeks 2 and 3; and 1/7 due to severe drowsiness.

Outcome measures were made at weeks 4, 8, 12, and 16 using the Paulus criteria, where a positive response is 20 percent change from baseline in four of six criteria: ESR, morning stiffness, joint pain and swelling count and score, and patient and physician global assessment. Two of the four patients in the placebo group had a Paulus 20 percent response at week 12, which was sustained through week 16. Of the 4/8 thalidomide-treated patients who remained in the study at week 4, 1/4 had clinical improvement that was sustained into week 12 but not week 16; 1/4 had clinical response at week 8 but withdrew secondary to peripheral neuropathy. Using an intent-to-treat analysis, there was no difference between the placebo and thalidomide groups at any followup time point. The average plasma TNF-alpha levels among all patients were elevated at baseline. However, there was no correlation between TNF-alpha levels and the severity of disease activity for all patients, nor was there a decrease in individuals who responded to thalidomide by Paulus criteria. The authors' experience indicates that future studies of thalidomide will require lower doses in an attempt to minimize toxic effects.

The Potential Application of Thalidomide for the Treatment of Inflammatory Bowel Disease

Robert H. Gelber, M.D.

The inflammatory bowel diseases of ulcerative colitis and regional enteritis, or Crohn's disease, remain major causes of severe gastrointestinal morbidity and, at times, mortality. Symptoms include abdominal pain, fever, diarrhea (at times bloody), weight loss, and abdominal distention. Both ulcerative colitis and Crohn's disease are marked by chronicity and by the need, in some cases, for surgical intervention and bowel resection. Ulcerative colitis is a premalignant condition, the risk of colon cancer being a function of disease duration and extent of colonic involvement. Therapy for inflammatory bowel disease centers on aminosalicylates (sulfasalazine or azulfidine) and corticosteroids as well as, in refractory cases, 6-mercaptopurine and azathioprine. These therapies are, unfortunately, not fully effective in all patients and are associated with significant toxic effects. Newer therapeutic modalities would be welcome.

Waters and colleagues (1979) described a young Malaysian Indian female with a 4-year history of ulcerative colitis refractory to therapy with sulfasalazine, hydrocortisone-retention enemas, and oral corticosteroids, whose disease resolved symptomatically and histologically on 400 mg of thalidomide daily. Her hemoglobin, which had been 8.9 g/dL, rose to 13.2 g/dL, and her gastrointestinal symptoms did not recur, although the prednisone and sulfasalazine were stopped at 5 months and 15.5 months, respectively, and the thalidomide dosage was reduced to 200 mg daily.

It was not until 1993 that Cohen and colleagues reported the further use of thalidomide in inflammatory bowel disease. They treated two patients who were unresponsive to conventional therapy—one with ulcerative colitis and one with Crohn's disease—with 100 mg of thalidomide three times daily. Both responded impressively for a few months, but, ultimately, while maintained on thalidomide, their inflammatory bowel disease relapsed. There are a few other published experiences in the adult and pediatric literature of cases of regional enteritis, ulcerative colitis, and Behçet's colitis treated with thalidomide, all with salutary responses. These will be presented.

The etiologies of inflammatory bowel diseases remain obscure. In both Crohn's disease and ulcerative colitis, there is an increase in the number and density of mononuclear cells in the lamina propria. Despite permanent stimulation by bacteria and food, intestinal lymphocytes normally are unresponsive to such antigens. However, recent studies demonstrate, in both Crohn's disease and mouse models of inflammatory bowel disease, that activated lymphocytes to gut flora and food are pathogenic. Both humoral- and cell-mediated components of the immune system have been implicated as important mechanistically in clinical inflammatory bowel disease and more recent murine models. Of relevance for a possible role of thalidomide in the therapy of inflammatory bowel disease, the intestinal mucosal production of tumor necrosis factor-alpha (TNF-() has been found to be increased in both Crohn's disease and ulcerative colitis, while fecal TNF-(, which is highly augmented in active chronic bowel disease, returns to normal during

remission. Recently, murine models of inflammatory bowel disease have been created in IL-10 knock-out mice, IL-2 deficient mice, and CD4-reconstituted SCID mice, a central role played by TNF-(and microbial flora in these models having been established.

In summary, although there is a limited, albeit beneficial, clinical experience with thalidomide in the treatment of inflammatory bowel disease, there have been compelling immunopathologic findings that suggest a possible role for thalidomide in these disorders. Controlled clinical trials appear in order.

A Phase II Trial of the Antiangiogenic Agent Thalidomide in Patients With Recurrent High-Grade Gliomas

Howard A. Fine, M.D.

More than 30 years ago, thalidomide was introduced into the clinic as a sedative but was quickly removed when its teratogenic effects were discovered. Recently, it has been demonstrated that thalidomide has potent antiangiogenic activity in vivo, a property that may be related to its mechanism of teratogenesis. Secondary to excellent oral bioavailability and minimal side effects, thalidomide is a promising antiangiogenic agent for long-term therapy in patients with angiogenic tumors. The author and colleagues, therefore, conducted a Phase II trial of thalidomide, administered as a daily 1,200-mg dose, in patients with recurrent high-grade astrocytomas and mixed gliomas.

To date, 32 of an expected 35 patients have been accrued, all of whom are evaluable for toxicity and 10 of whom are evaluable for response. Major toxic effects clearly related to the drug were extreme somnolence (three patients) and a drug rash (one patient). Other adverse events included seizures (five patients, two of whom had no prior history of seizures), deep venous thrombosis (one patient), and unexplained fever (one patient). Minimal radiographic responses were seen in four evaluable patients, several of whom have remained on thalidomide from 4 to 10 months since tumor recurrence. Extensive thalidomide pharmacokinetics and serial assays for biologic markers of angiogenesis (i.e., basic fibroblastic growth factor) have been evaluated in all patients; the results are still pending. In summary, thalidomide is one of the first antiangiogenic agents to be studied in a prospective trial of patients with malignant gliomas, and preliminary results suggest that it is well tolerated and appears to have some biologic activity at the currently used dose schedule.

A Randomized Phase II Study of Thalidomide in Androgen-Independent Prostate Cancer

William D. Figg, Pharm.D., Mike Hamilton, Raymond Bergan, Anne Tompkins, Alice Chen, Marston Linehan, Paul Duray, and Eddie Reed

Thalidomide is a potent teratogen that has been shown to inhibit angiogenesis induced by basic fibroblast growth factor in the rabbit cornea model (Proc Natl Acad Sci USA, 1994; 91:4082-5). Bauer and colleagues demonstrated inhibition of angiogenesis in several model systems only when thalidomide was coincubated with liver microsomes, suggesting that a metabolite of thalidomide is responsible for the activity.

We are evaluating two dosing regimens of thalidomide in this study (200 mg/d vs. 1,200 mg/d). Twelve patients with androgen-independent prostate cancer have been enrolled (six high dose and six low dose; median age, 66.5 years [range 50 to 80], median Gleason 8 [range 6 to 9], median ECOG performance status 1 [range 0 to 1]). All patients had bone metastasis, and eight patients had soft tissue disease. All had failed combined androgen deprivation, and seven patients had failed secondary hormonal manipulations. Pharmacokinetic analysis revealed a half-life for thalidomide of 13.1 ± 14.5 h, clearance (CL/F) of 7.1 ± 3.7 L/h, and a volume of distribution (VD/F) of 88.9 ± 44.5 L. Steady-state concentrations for the high-dose group have averaged >10µg/mL.

Two patients had grade 3 complications (neuromotor and constipation), with the remaining complications limited to grade 1-2 (dizziness, drowsiness, xerostoma, neurosensory, and rash). Four patients (30 percent) have had PSA declines (between 20 percent and 37 percent declines in each group), with the longest maintained for 84 days. Six patients have progressed (28, 53, 62, 64, 74, and 84 days). The objective is to enroll 14 patients in each arm of the study, with possible extension of one arm if activity is noted. The group receiving the highest dose appears to have a subjective benefit more often than the lower dosage group.

Thalidomide Treatment of Graft-Versus-Host Disease

Georgia B. Vogelsang, M.D.

Chronic graft-versus-host disease (GVHD) is the most common late complication of allogeneic bone marrow transplantation. Approximately 40 percent of patients surviving the first 100 days post-transplant will develop this complication. About one-half of the patients developing chronic GVHD will die of their disease or complications (mainly infectious) of it. Therapy for chronic GVHD has relied on steroids, most commonly given with CsA. Other agents that have been used include azathioprine, total lymphoid irradiation, FK-506, PUVA, and ATG. Although responses have been seen with each of these agents, many patients have persistent and/or progressive disease. The use of alternative donors (matched unrelated donors and mismatched related donors) and older age patients have dramatically increased. These two patient populations are at increased risk for the development of chronic GVHD. Thus, chronic GVHD continues to be a very important problem.

We have reported on thalidomide treatment of patients with either high risk (< 20 percent survival predicted by the presence of markers of poor outcome) or refractory chronic GVHD. Patients had their current GVHD regimen maintained for 3 months while starting on thalidomide 200 mg q.i.d. Of the 44 patients in the initial report, 59 percent responded to treatment. Survival for the entire cohort of responders and nonresponders was 64 percent. The primary cause of death was infection. Most deaths were early, occurring within several months of starting on protocol. Only three patients have relapsed with their primary malignancy, suggesting that thalidomide has not caused a loss of the graft-versus-leukemia effect. Several other groups have reported similar promising results, and results from these groups will be reviewed. One large study from the City of Hope transplant group failed to show as substantial a benefit. The Stanford University transplant group also examined the use of thalidomide in preventing chronic GVHD in patients with prior acute GVHD (i.e., prophylaxis of chronic GVHD) and found that thalidomide was not useful in that setting.

We are currently examining combination therapy for the treatment of high-risk and refractory chronic GVHD. The purpose of this study is to determine whether the response rate is improved by offering combination therapy, a short course of PUVA (UVA light plus psoralen), and combined cyclosporine and thalidomide while decreasing the infection risk by limiting steroid usage.

The ultimate utility of thalidomide in treatment of chronic GVHD is not known. Although multiple studies have suggested a beneficial effect, others have been disappointing in their results. Further clinical trials should better define thalidomide's role in GVHD.

Preliminary Results of a Phase II Dose Titration Study of Oral Thalidomide in Patients With HIV Infection and Kaposi's Sarcoma

Rich Little, Lauri Welles, Kathleen Wyvill, James Pluda,William Figg, Giovanna Tosato, and Robert Yarchoan, M.D.

Background

Neovasularization and angiogenesis are important in the pathogenesis of Kaposi's sarcoma (KS). Thalidomide is an oral drug that has been shown by D'Amato, Folkman, and colleagues to inhibit angiogenesis in a rabbit cornea assay. It has immunomodulatory properties but is not associated with bone marrow suppression.

Methods

A Phase II dose titration trial of oral thalidomide administered for up to 52 weeks was initiated. Entry requirements included cutaneous KS lesions with evidence of disease progression in the 2 previous months. Dosing started at 200 mg per day with escalation every 2 weeks, as tolerated, to a maximum of 1,000 mg per day. A minor modification of the AIDS Clinical Trials Group KS criteria was used to assess responses.

Results

Nine patients have accrued to date. Demographics include male = 9, white = 8, black = 1; median (range) age = 41 (32-49) years; entry median (range) CD4 counts = 214 (13-741) cells/mm^3. Using the TIS staging (JCO 7:1201,1989) strategy for KS, six were poor risk, and three were good risk. To date, three patients, all poor risks by TIS criteria, have attained a partial response (PR) based on ≥50 percent decrease in the number of nodular lesions sustained for at least 4 weeks (response rate 33 percent). One patient who achieved a PR was started on triple antiretroviral therapy after beginning thalidomide. Two of these patients had received prior systemic cytotoxic chemotherapy. These responses were first observed at weeks 4 (2/9) and 8 (1/9) at daily doses of 300 mg, 400 mg, and 800 mg. One of these patients also had psoriasis, which appeared to improve along with the KS. Two patients still had not progressed at 42 and 35 weeks, while one of the patients achieving a PR progressed after 26 weeks. One patient progressed without achieving a PR after 8 weeks, while four patients have had stable disease to date. Of those, one patient had no evidence of progression for 52 weeks, two had stable disease on study at 12 weeks, and one had stable disease at 4 weeks. One patient had a grade 3 rash with fever that recurred with drug rechallenge and was not evaluable for response. Three patients had grade 3 neutropenia on study. The only dose-limiting toxicity was sedation, which occurred in four patients and resolved with a dose reduction. Inducible protein-10 (IP-10) levels appeared to increase in one of five patients in which this parameter was measured.

Conclusion

Thalidomide is well tolerated in patients with HIV infection and KS at doses of up to 1,000 mg per day. This drug appears to be active in KS and, in some cases, to induce durable responses. This trial is ongoing, and further study will help define the potential role of thalidomide in the therapy of KS.

Reference

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Phase II Evaluation of Thalidomide in Patients With Metastatic Breast Cancer

Said Baidas, M.D.

Breast cancer is the most common cancer in women in North America, with 185,000 new cases and 44,500 deaths in 1996. Metastatic breast cancer is considered incurable with current therapies. Standard therapies include chemotherapy, hormonal therapy, or a combination of both. Although initial response to therapy is high, all tumors eventually develop resistance and can no longer be controlled. Thus, it is imperative to develop new treatment strategies such as the use of antiangiogenesis agents. Several studies suggest that microvascular quantitation within breast cancer might be one of the prognostic tools for tumor growth and metastasis. Therefore, inhibition of angiogenesis is an attractive mode of therapy in breast cancer. The recent report of the antiangiogenic activity of thalidomide by D'Amato and Folkman suggests it might be useful for the treatment of breast cancer.

Antiangiogenic therapy will require prolonged use of an active agent to achieve the therapeutic goal. Thalidomide given in the oral form, with tolerable side effects, makes it attractive for this form of therapy. Phase II Evaluation of Thalidomide in Patients With Metastatic Breast Cancer is a multicenter study. Patients with metastatic breast cancer are randomly assigned to receive thalidomide at either a low dose (200 mg/d) or high dose (800-1,200 mg/d). The primary objective of this study is to assess the difference in activity and in safety profile between the low-dose and high-dose arms of thalidomide. The following secondary objectives will also be evaluated: (1) to determine the response rate, (2) to compare pretreatment and posttreatment growth rates, (3) to study growth factors expressions in patients receiving thalidomide, and (4) to study thalidomide pharmacokinetics. Eligible patients must have progressive measurable or evaluable metastatic disease and have received no more than three chemotherapy regimens for both adjuvant and metastatic disease.

Thalidomide as Immunomodulatory Adjunctive Therapy in Tuberculosis

Gilla Kaplan, Ph.D.

Tumor necrosis factor-alpha (TNF-α) plays a central role in the regulation of the protective granulomatous response in chronic infections such as leprosy and tuberculosis. The cytokine is produced by leukocytes in response to exposure to the mycobacteria and their components. However, TNF-α production is also associated with pathologic manifestations of these diseases, including fevers, weight loss, and tissue damage. It has recently been observed that when patients with advanced pulmonary tuberculosis begin antibiotic treatment, there are an initial clinical worsening and a weight loss that correspond with a transient increase in plasma TNF-α levels. The reduction in TNF-α levels observed by 14 days post-initiation of tuberculous therapy is associated with weight gain and clinical improvement. Because thalidomide has been shown to be a selective partial inhibitor of TNF-α , the use of this drug has been studied in clinical situations in which TNF-α contributes to disease pathogenesis.

Initial pilot studies were carried out on patients with pulmonary tuberculosis who had already begun antibiotic treatment. These patients received a 14-day course of thalidomide (300 mg/d) together with the antibiotics. Thalidomide treatment was well tolerated, and there were no serious adverse events. During the period of thalidomide treatment, the patients experienced an accelerated weight gain of about 6 percent of starting body weight. This weight gain was associated with a reduction in TNF-α as well as TNF-α mRNA levels and an increase in IFN-γ levels in the blood. It is important to note that thalidomide treatment did not result in any observed immune suppression.

These observations were confirmed in a further study of patients coinfected with tuberculosis and HIV. In dually infected patients treated with antibiotics and thalidomide (300 mg/d) for 21 days, there was an 8 percent increase in mean body weight from starting weight. A positive correlation between plasma TNF-α levels and HIV-1 levels was observed in these patients.

In ongoing placebo-controlled blinded studies, the author is investigating the effects of thalidomide on clinical outcome, TNF-α levels, HIV-1 load, and wasting in patients with concomitant HIV-1 and tuberculosis infections. Also being studied are the effects of thalidomide in children with tuberculous meningitis.

HIV/AIDS Wasting Syndrome

Morris Schambelan, M.D.

Body wasting frequently accompanies HIV infection and is an increasingly important factor in the survival of affected individuals. Although the pathogenesis of wasting is multifactorial, considerable attention has been focused on the metabolic disturbances seen typically in such patients. For example, increases in resting energy expenditure (REE) have been repeatedly documented in patients at all points along the spectrum of HIV infection. However, not all HIV-infected individuals are hypermetabolic, and quantitative analysis demonstrates that hypermetabolism alone cannot explain the magnitude of loss of body weight in HIV infection. An increasing body of evidence indicates that reduced energy intake, and not increased energy expenditure, is the prime determinant of weight loss in HIV-associated wasting, particularly in association with acute infections. Despite this, strictly nutritional therapies have not been generally successful in reversing the loss of body weight and of lean body mass (LBM) that occurs in more advanced stages of HIV infection. Pharmacologic doses of recombinant human growth hormone can increase LBM, but this therapy does not address the underlying pathogenetic mechanisms.

Increased levels of proinflammatory cytokines have been observed during HIV infection, especially during advanced stages. Cytokine disturbances have been implicated in the metabolic disorders that accompany HIV infection. Although no studies to date have mechanistically linked specific cytokines with wasting per se, it is generally thought that a combination of cytokines is probably contributing to the disturbances in energy balance noted in HIV-infected individuals. Relatively weak suppressors of cytokine production have not proven effective in patients with HIV infection. Dietary n-3 fatty acids, which reduce the production of IL-1 and TNF-(by PBMCs in normal subjects and prevent anorexia caused by IL-1 and TNF-(in experimental animals, failed to alter energy intake, body weight, percentage fat, or fat-free mass, during a 10-week period, in relatively stable subjects with no secondary infection. Similarly, pentoxifylline, which causes a significant decrease in TNF-(mRNA levels in PBMCs, also failed to produce weight gain in small clinical trials.

Thalidomide, which has proved to be remarkably effective in the treatment of oral aphthous ulcers in HIV-infected patients, promoted weight gain in the setting of HIV infection complicated by active tuberculosis. In a study conducted in both New York and Thailand, an average weight increase of 6 percent in only 2 weeks was noted in patients with tuberculosis (with and without HIV infection) who received thalidomide (300 mg) compared with only 2 percent in those given a placebo. Even more striking differences were noted in a subsequent study of patients with HIV infection, both with and without tuberculosis. Weight gain in those with HIV infection alone averaged 4 percent, and, in those patients co-infected with tuberculosis, 8 percent improved after only 3 weeks of treatment with thalidomide. These increases were significantly different from the responses seen in the placebo-treated subjects in both subgroups; patients with tuberculosis who received placebo lost weight during these 3 weeks, despite initiation of standard antituberculous therapy.

Two placebo-controlled trials have evaluated thalidomide in the stable patients with HIV-associated wasting. In a study performed in Mexico, weight gain was reported in 8 of 14 patients treated with thalidomide (100 mg, four times daily) for 12 weeks, compared with only 1 of 14 in the placebo group. Preliminary results from a multicenter randomized trial (Celgene W-001) that compared two doses of thalidomide (100 and 200 mg/d) and placebo in a total of 99 patients indicate a significant weight gain (3.3 percent) at 8 weeks in those given 100 mg, but a less robust effect at the higher dose (intent-to-treat analysis) because of a higher dropout rate. At least half of the weight gained was in the form of LBM. Side effects included drowsiness, rash, declines in neutrophil count, and a modest, and probably transient, increase in HIV-1 RNA levels.

Thalidomide for the Treatment of Oral Aphthous Ulcers in Patients With Human Immunodeficiency Virus Infection

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ABSTRACT

Background. In patients with advanced human immunodeficiency virus (HIV) infection, aphthous ulceration of the mouth and oropharynx can become extensive and debilitating. Preliminary reports suggest that thalidomide may promote the healing of oral aphthous ulcers.

Methods. We performed a double-blind, randomized, placebo-controlled study of thalidomide as therapy for oral aphthous ulcers in HIV-infected patients. The patients received a 4-week course of either 200 mg of thalidomide or placebo orally once per day. They were evaluated weekly for the condition of the ulcers, their quality of life, and evidence of toxicity. Assays were performed for plasma tumor necrosis factor-alpha (TNF-(), soluble TNF-(receptors, and HIV RNA.

Results. Sixteen of 29 patients in the thalidomide group (55 percent) had complete healing of their aphthous ulcers after 4 weeks, as compared with only 2 of 28 patients in the placebo group (7 percent; odds ratio, 15; 95 percent confidence interval after adjustment for group sequential testing, 1.8 to 499; unadjusted $P < .001$). Pain diminished and the ability to eat improved with thalidomide treatment. The adverse effects noted with thalidomide included somnolence and rash (7 patients each), and 6 of the 29 patients discontinued treatment because of toxicity. Thalidomide treatment increased HIV RNA levels (median increase, 0.42 $\log_{10}$ copies per milliliter; increase with placebo, 0.05; $P = .04$). With thalidomide treatment, there were unexpected increases in the plasma concentrations of TNF-(and soluble TNF-(receptors.

Conclusions. Thalidomide is an effective treatment for aphthous ulceration of the mouth and oropharynx in patients with HIV infection. (N Engl J Med 1997;335:1487-93).

The Neurology of AIDS

Howard E. Gendelman, M.D.

HIV enters the brain soon after virus exposure but elicits profound neurological deficits in infected individuals years later, usually during progressive immunosuppression and the development of AIDS. The neurological disease complex associated with viral infection occurs in a significant proportion of infected patients and is commonly referred to as HIV-1-associated dementia complex. The neuropathogenesis of central nervous system infection revolves around immune activation and persistent HIV-1 replication in mononuclear phagocytes (brain macrophages and microglia). Macrophages secrete neurotoxic factors that elicit neuronal injury, and inevitably death, leading to the constellation of cognitive and motor impairments during progressive disease. Neurotoxic factor production requires viral entry and replication and consists of both viral gene products and cellular immune factors.

We will review, in this presentation, the constellation of secretory products from mononuclear phagocytes that underlie neurodegeneration in HIV dementia. Pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha) are central in this process. Our laboratory, animal model, and clinical interventional studies will highlight the role of immune regulatory events in HIV neuropathogenesis. Model systems of the blood-brain barrier, primary microglial infection model, a SCID mouse system for HIV encephalitis, and the reversal of HIV dementia in an infected patient will be discussed.

INFORMED CONSENT TEMPLATE
(Revised 8/14/97)

TITLE
(Thalidomide for the Treatment of _____)

IMPORTANT INFORMATION AND WARNING:

It is important for you to know that thalidomide is known to cause severe birth defects if it is taken by a pregnant female. Therefore, it is important that thalidomide not be used by females who are pregnant or could become pregnant while undergoing treatment with this drug.

Thalidomide is also known to cause nerve damage that may be permanent.

Thalidomide is not approved for use in the United States. However, the Food and Drug Administration (FDA) allows restricted use of thalidomide as an investigational treatment of certain severely debilitating or life-threatening diseases, and for treatment of certain diseases for which there is no alternative treatment.

INFORMED CONSENT:

Because you have _____, you are invited to volunteer to be treated with an investigational drug called thalidomide. Before you decide whether or not to volunteer to take thalidomide to treat your condition, it is important that you understand how thalidomide may help you, the risks to you, and what would be expected of you. This process is called informed consent.

YOUR RIGHTS:

This consent form gives you information about the use of thalidomide. After you have been informed about this drug by your doctor (Sponsor-Investigator), and if you agree to volunteer, you will be asked to sign this consent form. You will be given a copy to keep.

It is important for you to know the following: Your participation is voluntary. You may choose not to participate in this study without penalty or loss of benefits or treatment to which you are entitled. Likewise, if you choose to participate, you may withdraw at any time without penalty or loss of benefits or treatment to which you are entitled.

PURPOSE:

The purpose of this study is to gather information about the safety and potential benefit of thalidomide to you and to others with your condition.

BACKGROUND:

Typical Disease Presentation (to be completed by Sponsor-Investigator)

Evidence Supporting Use (to be completed by Sponsor-Investigator)

Thalidomide is believed to act on the immune system to correct a response that is harmful (for example, when the immune system attacks normal cells in the body), or when a response is out of control (excessive inflammation). You have been offered the opportunity to use this medication because this type of immunologic activity may help to control or improve your current condition. However, you should remember that this is an experimental drug therapy. Thalidomide may not help you and it may hurt you.

PROCEDURES:

If you decide that you want to take thalidomide and sign this consent form, you will have the following laboratory tests and examinations to evaluate your eligibility for the study and to monitor your response to the drug: _____. If you participate in this study, your treatment will last for up to _____. You will be seen by your doctor (Sponsor-Investigator) every _____ for _____ months. For your condition, you will take thalidomide ____ times a day for _____ weeks.

The following conditions have been set up to guide your doctor (Sponsor-Investigator) in determining who may receive thalidomide:

* you must have no significant nerve damage in your arms or legs on physical examination;

* if you are a female and physically able to have children: (1) you must not be pregnant or be nursing a child; (2) you must refrain from activities intended to result in pregnancy (e.g., fertilization methods); and (3) you must abstain from reproductive sexual intercourse, or use two highly effective birth control methods at the same time for at least one month prior to receiving thalidomide, and continuing regularly thereafter until one month after the last dose;

* if you are a male who has not had a vasectomy, you must abstain from reproductive sexual intercourse, or use a condom during intercourse while receiving thalidomide, and continuing thereafter until one month after the last dose.

RISKS AND/OR DISCOMFORTS:

You should tell your doctor (Sponsor-Investigator) or your health care-provider if you have any unusual symptoms while taking thalidomide.

BIRTH DEFECTS:

Thalidomide causes severe birth defects in unborn babies if it is taken by females who are pregnant. The risk of thalidomide causing damage to the embryo is up to 50% for females taking thalidomide during the "sensitive period," which is estimated to range from 35-50 days after the last menstrual period. It is not known whether thalidomide may cause birth defects in unborn babies if it is taken after the "sensitive" period. A single dose of thalidomide may cause birth defects.

Birth defects observed in babies exposed to thalidomide during pregnancy include absent or abnormal legs and arms; spinal cord defects; cleft lip or palate; absent or abnormal external ear; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system, including blockage of necessary openings.

Because of the severity of these abnormalities, it is extremely important that pregnancies do not occur while you are taking thalidomide. It is not known if thalidomide is present in male ejaculate (semen).

You should discuss with your doctor (Sponsor-Investigator) what the best methods of birth control are for you. Remember, however, that no method of birth control besides complete abstinence provides 100% protection from pregnancy.

If you are a female who is able to have children, you will be required to have blood drawn for a pregnancy test before you start taking thalidomide. If you have a positive pregnancy test, you will not be allowed to take thalidomide. While you are taking thalidomide, you will be required to have a pregnancy test 9-10 days after receiving your first dose of thalidomide, then once a month if you have a normal menstrual cycle; pregnancy testing will be done more frequently if your menstrual cycle is irregular. You will also be required to have a pregnancy test four weeks after you finish taking thalidomide. A pregnancy test will also be done whenever you miss a menstrual period.

If you suspect you are pregnant, you must IMMEDIATELY stop taking thalidomide. You should also IMMEDIATELY contact your doctor to determine if you are pregnant. If you become pregnant while taking thalidomide, you must IMMEDIATELY stop taking thalidomide and return the unused portion of thalidomide to your doctor. You should IMMEDIATELY contact your doctor to discuss your pregnancy. Your doctor is required to notify the FDA if any patient becomes pregnant while taking thalidomide.

NERVE DAMAGE:

Thalidomide might cause damage to your nerves. One of the symptoms of nerve damage may be numbness and tingling in the arms, hands, legs, and feet. This usually occurs after long-term use of the drug, but may occur during brief exposure to the drug. It is not known whether this nerve damage will go away after use of the drug is stopped. It is also not known whether other conditions, such as diabetes, certain skin disorders (such as prurigo nodularis), alcoholism, or the use of neurotoxic drugs, may increase the chance of developing nerve damage. You are at risk for permanent nerve damage when you take thalidomide.

ADDITIONAL SIDE EFFECTS:

Thalidomide frequently causes drowsiness (it was initially used in other countries as a sleeping pill). You should avoid drinking alcohol or taking other medications that also may cause you to be sleepy. [You should not operate machinery or participate in activities requiring alertness and clear judgement (for example, driving) while taking this drug.]

Another side effect of thalidomide may be the development of skin rashes. These rashes have sometimes occurred together with fevers, fast heart beat, itching, and low blood pressure. You should contact your doctor right away if you notice a skin rash while taking thalidomide.

It is not known what other effects thalidomide may have on the immune system, such as immune responses that protect the body from infection and cancer. In a May 22, 1997 article in the New England Journal of Medicine, increases in HIV viral load were described in HIV-infected patients who received thalidomide for the treatment of aphthous ulcers; it is unclear if this increase is clinically meaningful. Since this trial was conducted before the widespread use of highly active antiretroviral therapy(HAART), it is not known if increases in viral load will be seen in the setting of HAART. You should discuss treatment options with your doctor.

The following additional side effects may occur while taking thalidomide: neutropenia (low white blood cell count), hang-over, dizziness, mood changes, dryness of the mouth, headache, nausea, constipation, increased appetite, loss of sex drive, puffiness of the face and limbs, itching, dry skin, menstrual abnormalities (such as an irregular period), blood sugar variations (too high or too low), and thyroid problems. Any of these side effects should also be reported to your doctor.

Because it is not known how thalidomide reacts with other drugs, you should not take any other prescription or over-the-counter drug while taking thalidomide without first talking to your doctor.

POTENTIAL BENEFIT:

Participation in this program may help _____, but no guarantee can be made.

SAFEGUARDS:

You will be watched closely by your doctor during your participation in this study. If you have any serious reactions to thalidomide, the dose will be changed or the drug will be stopped to protect your health.

NEW FINDINGS:

While you are taking thalidomide, you will be told by your doctor of any new information learned that might cause you to change your mind about taking thalidomide.

REASONS FOR STOPPING THALIDOMIDE WITHOUT YOUR CONSENT:

For any of the following reasons, thalidomide may be stopped without your consent: (1) the doctor (Sponsor-Investigator) decides that continuing thalidomide would be harmful to you; (2) you fail to take treatments, keep appointments, or have laboratory tests as instructed (such as a pregnancy test); (3) you have a serious adverse reaction to thalidomide; (4) you become pregnant; (5) you fail to refrain from reproductive sexual intercourse or to use the methods of birth control prescribed by your doctor; (6) the study is stopped by the Food and Drug Administration or by the drug supplier.

ALTERNATIVES TO PARTICIPATION:

Before you decide to take thalidomide, you should know about other treatment choices available to you. These include: (Sponsor-Investigator to complete)

COST OR PAYMENTS TO YOU:

There is no cost to you for the thalidomide. But other medical costs, including clinic visits, examinations, or laboratory tests, will be charged to you or your health insurance company.

You will receive no payment for taking thalidomide.

CONFIDENTIALITY:

Because of the need to release certain information to other parties, absolute confidentiality about your use of thalidomide cannot be guaranteed. Records of your use of thalidomide will be confidential to the extent permitted by the law. Your records may be inspected by, or provided to the U.S. Food and Drug Administration and/or the drug supplier under guidelines of the Federal Privacy Act.

RESEARCH-RELATED INJURY:

If you are hurt as a result of your participation in this program, or become pregnant while participating in this program, your doctor will treat you if you need immediate attention or discuss therapeutic options with you. You or your health insurance company may have to pay for such treatment.

PROBLEMS OR QUESTIONS:

If you ever have questions about your participation in this study, your rights as a volunteer, or about a research-related injury, you should contact your doctor (Sponsor-Investigator), _____, at the following telephone numbers _____, _____, or the Institutional Review Board (IRB), at the following number _____.

VOLUNTEER CONSENT:

Thalidomide must be taken only by the person for whom it has been prescribed and it must be kept out of reach of children. It is important that thalidomide be kept away from females who are able to have children.

I have carefully reviewed the contents of this form. I have had an opportunity to ask my doctor (Sponsor-Investigator) questions about thalidomide and my participation in this study. I give my voluntary informed consent to participate. By signing this form, I have not waived any of the legal rights that I otherwise would have.

FEMALES ABLE TO BEAR CHILDREN: Profound birth defects to unborn children often occur when mothers take thalidomide during pregnancy. I understand that I must have a negative pregnancy test before, during, and one month after stopping thalidomide. I agree to refrain from any activities that could result in pregnancy or to practice effective birth control while taking thalidomide. I agree to immediately stop taking thalidomide and inform my physician if (1) I think that I am pregnant, (2) I engage in reproductive sexual intercourse and stop using birth control, or (3) I become pregnant.

_____	_____	_____
Volunteer's Name (Print)	Volunteer's Signature	Date

OR

_____	_____	_____
__Volunteer's Legal Guardian __or Legal Representative	Legal Guardian's or Representative's Signature	Date

_____	_____	_____
Witness' Name (Print)	Witness' Signature	Date

I have explained to the volunteer the purpose of participation in this study, and have answered the volunteer's questions about thalidomide and her or his participation in the study. To the best of my knowledge, s/he understands the purpose, procedures, risks, and benefits of this treatment program.

_____	_____	_____
Doctor's Name (Print) (Sponsor- Investigator)	Doctor's Signature (Sponsor-Investigator)	Date

Note to Sponsor-Investigator: The original signed consent form must be retained in the patient's record; copies of the signed form must be provided to the patient or the patient's legal guardian or representative, the Institutional Review Board, and the Food and Drug Administration.

GENERAL GUIDELINES FOR ALL PATIENTS:

Thalidomide has been prescribed only for you.

Do not share it or give it to others. It can be extremely harmful if used by others.

Be sure to take your medication as prescribed by your doctor. If there is anything you do not understand, ask your doctor to explain it to you.

Thalidomide often causes drowsiness. You should avoid drinking alcohol or taking other medications that also make you sleepy. Your ability to operate machinery or participate in activities requiring alertness and clear judgment (for example, driving) may be impaired while taking thalidomide.

Thalidomide might cause damage to your nerves. It is not known whether this nerve damage is reversible after the drug is stopped. Symptoms of nerve damage include burning, numbness, or tingling of your arms, hands, legs, or feet. Call your doctor if you have any questions or experience any of these severe or other troubling symptoms.

Your doctor may do special laboratory tests to check for nerve damage.

Check with your doctor before taking any other prescription or over-the-counter medication.

If you develop a skin rash with or without a fever, fast heart beat, or low blood pressure, immediately stop taking thalidomide and contact your doctor.

Any side effect should be reported to your doctor. The following list contains additional side effects that may occur while you are taking thalidomide:

mood changes
dry mouth
headache
nausea
constipation
increased appetite
puffiness of the face and limbs
dry skin
itching
irregular menstrual period
low white blood cell count
thyroid problems
blood sugar that is too high or low
slow heart beat

For females, you will be required to have a blood or urine test for pregnancy on a monthly basis or more frequently if you have irregular menstrual periods. Pregnancy testing will also be done if you experience vaginal bleeding or if you miss a menstrual period.

You must return any unused thalidomide to your doctor.

FDA

HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE • FOOD AND DRUG ADMINISTRATION

DHHS Publication No. (FDA) 96-3222

Thalidomide

IMPORTANT PATIENT INFORMATION

Thalidomide may be the most infamous drug in recent history. In the late 1950's, thalidomide was marketed in Europe as a sleeping pill and used to alleviate morning sickness during pregnancy. Tragically, however, its use by pregnant women resulted in the birth of thousands of deformed babies. In 1961, scientists discovered that the medication stunted the growth of fetal arms and legs. In fact, taking only one dose of thalidomide early in pregnancy can severely affect the growth of fetal limbs (arms, legs, hands, feet). It also puts the fetus at risk of other injuries, including eye and ear defects; and severe internal defects of the heart, genitals, kidneys, digestive tract (including lips and mouth), and nervous system.

Thalidomide is not approved for use in the United States. However, the Food and Drug Administration allows restricted

investigational use of thalidomide to treat certain severely debilitating or life-threatening diseases and certain other diseases for which there is no alternative treatment.

The purpose of this investigational program is to attempt to treat your condition because you have a severe illness that has not responded to other therapies, and to gather information about the safety and the potential benefit of thalidomide.

While you are taking thalidomide, you will be told by your doctor of any new information that might cause you to change your mind about taking thalidomide.

WARNING FOR FEMALE PATIENTS:
JUST ONE THALIDOMIDE PILL CAN CAUSE BIRTH DEFECTS

You must not take thalidomide if you cannot avoid pregnancy.

You must have a blood or urine test done by your doctor that shows you are not pregnant, before you may take any thalidomide.

You must abstain from sexual intercourse or use two highly effective birth control methods at the same time (consult your doctor), for at least one month prior to receiving thalidomide, and continuing regularly thereafter, until one month after the last dose of thalidomide.

Remember, no method of birth control is completely reliable except for having no sexual intercourse at all (abstinence).

If you do not practice abstinence or you have not had a hysterectomy, you must use birth control even if you believe you cannot become pregnant.

You must also refrain from any other activities that could result in pregnancy (for example, fertilization methods).

You must not take thalidomide if you are nursing a baby.

You must immediately stop taking thalidomide and inform your doctor if:

- You have **a late or an irregular** menstrual period
- You **stop practicing** abstinence
- You **stop** using birth control
- You **think** that you are pregnant
- You **become** pregnant.

If you become pregnant, **you must *immediately* stop taking thalidomide.** You should contact your doctor to discuss whether or not to continue your pregnancy.

WARNING FOR MALE PATIENTS:

You must be willing to abstain from sexual intercourse or use a condom during intercourse while you are taking thalidomide and for at least one month after the last dose of thalidomide, because it is not known if thalidomide is present in male ejaculate (semen).